Genetic Resistance to Disease in Domestic Animals

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To Randall Knight Cole

Preface

THIS little book is the outgrowth of a series of lectures given at North Carolina State College in 1956 They in turn, grew out of my interest for three decades in the desirability and feasibility of breeding domestic animals that can withstand ordinary levels of exposure to disease As a result of our studies here at Cornell University that interest at first little more than commendable curiosity has become a firm conviction that the biological fitness of domestic animals to cope with their environment, including disease can be greatly increased by selective breeding

It is true that my own work on resistance to disease has been limited to my favorite species. However in order to inoculate my veterinary students, whose preferences among domestic animals rarely include the fowl, it has been an absorbing necessity to keep informed on genetic resistance to disease in all domestic animals. Accordingly while I have faithfully exercised the scientific virtue of citing my own research without any subtle beating about the bush, it has been possible to supplement those citations in this book, as in my lectures, with a review of what little is known about resistance to disease in other animals.

If it should seem to the reader that too much of this book

is devoted to a marshaling of the evidence that animals do differ genetically in resistance to disease and that too little of it deals with the actual practical use of that resistance let him remember that the chief purpose of the volume is to provoke some thinking perhaps some controversial discussion, and eventually more research. If it succeeds in attaining these objectives, those who write later and better books on the same subject will have more to say about applications.

I am indebted to my colleague Dr R K. Cole, who read parts of the manuscript and made many helpful suggestions. I shall also be indebted to any readers who may be so kind as to report any conspicuous sins of omission or commission

It seems a pity to toss this little book to those ubiquitous and inevitable arbiters—the reviewers. It has about as much chance as a turtle trying to cross Chicago's Michigan Boulevard. The veterinarians are likely to condemn it because of its rank heresy and because the author who is not a veterinarian, should not have ventured to write about disease Similarly the authorities in animal husbandry will probably tear it apart, page by page because the author a mere chicken expert, should have stuck to his field, which is clearly poultry and not animals. Animals, as defined by the administrators of agricultural colleges and of country fairs are horses, cattle sheep swine and goats, while poultry are chickens, turkeys, rabbits and canaries In defense against the impending onslaught, the author can plead only that he wrote the book because none of those others who should have written it seemed much interested in doing so It is to be hoped that its critics will at least find it interesting

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Chapter I

Why and Wherefore

IT seems desirable to begin by stating some of the reasons that led to the writing of this book. All geneticists are interested in variation Some of us are concerned with variation in domestic animals, particularly with their differ ing abilities to produce milk, butterfat, eggs, meat, wool, or work. To measure adequately genetic differences in produc tivity one must provide an environment conducive to the best possible performance by the animals under study That optimum environment must include some degree of physical comfort. This is often assured by some simple shelter from the elements, is sometimes improved in specially ventilated and air-conditioned quarters, and, if we can believe what we read in the newspapers may occasionally be enhanced by the administration of soothing selections from the nearest broadcasting station. The food supply must be adequate, both in quantity and quality for the purpose intended. Thanks to the good work of the experts in nutrition there is now little difficulty in providing a satisfactory diet for most species, for most purposes, in most parts of North America.

Finally if the animals are to demonstrate what their genes

permit them to do in the way of converting feedstuffs to milk, meat, or eggs, it is necessary that they be plagued by no more bacteria viruses, parasites, and other organisms than they can tolerate without adverse effects upon their normal physiological processes Here the problem is not so simple

It would be nice for the farmer if all pathogenic organisms could be eradicated, but attempts to eradicate them have not been uniformly successful. The prospects of our attaining this utopian state of affairs are no better than are those of paying off the national debt. Programs for eliminating bovine tuberculosis have apparently been successful in this country and happily so because some human beings are susceptible to bovine tuberculosis One wonders however to what extent the causative bacillus is still carried by deer whether or not it will ever be feasible to stop testing and, also what may happen a thousand years hence if cattle unexposed for that time again encounter the organism

Attempts to eradicate *Brucella abortus* have not fared so well as the campaigns against *Mycobacterium tuberculosis* Blood-tested herds from which all reactors are removed remain clean for a time but when reinfected as frequently happens, they seem unusually susceptible The resort to vaccination which is now the more common method of control, suggests that the earlier attempt to eradicate *B abortus* was not too successful. Vaccinated animals can live with the organism. Some cattle are undoubtedly able to do so without protective vaccination, but unless and until whole herds are made genetically resistant vaccination will continue to provide effective control at comparatively low cost.

Chickens vaccines and genes In other cases vaccination can be an expensive nuisance. To protect the author's White

Leghorns from the various respiratory diseases prevalent in his part of the world, a maker of vaccines advises the following treatments

Against Newcastle disease Three inoculations intranasally or in the drinking water by 16 weeks of age

Against infectious bronchitis Two treatments, which can be given along with two of those for Newcastle disease

Against fowl pox (*a*) vaccination once in the web of the wing, or (*b*) pigeon-pox vaccine (in a feather follicle) followed 10 days later by fowl pox vaccine

Against laryngotracheitis vaccination once in the cloaca.

By these five to eight treatments, administered fore aft and amidships, the birds would presumably be protected against these four respiratory diseases. For a fifth one, *infectious coryza there seems to be no effective vaccine and* the usual recommendation when that strikes is to depopulate (i.e. market the whole flock) clean and disinfect the premises, leave them vacant for several weeks or months and then start over with a new batch of chicks.

In addition to these five respiratory diseases, there is chronic respiratory disease, which we are currently advised to eliminate by dosing our breeding flocks with antibiotics, so that they will not put the causative organism in their eggs. Should any chicks thus hatched free of that pleuropneumonia like organism subsequently react to tests for it, they and the rest of the chickens in their pen can be slaughtered.

For the commercial poultryman some or all of these procedures may be indispensable if he is to remain in business with the kind of stock now available to him. Vaccines differ however as do directions for using them and there is no assurance of complete freedom from respiratory diseases.

The author having seen all six of these respiratory diseases go through his flocks at one time or another (*fortunately*

not all at once) doubts that such elaborate protection is necessary Certainly some birds need it, but others do not. While some hens die of these diseases or stop laying others in the same flock, in the same pen are completely unaffected and continue to lay well. Can it be that they are not exposed? Not likely It is much more probable that they are able to tolerate the infectious organisms, to resist them in some way and thus to withstand a bit of the environment that may be disastrous to other birds.

Can the resistant birds be multiplied to produce a resistant strain? They can if their resistance is determined by their genes and there is evidence that this is so. Within one breed two strains intermingled in the same flock can differ significantly in susceptibility to respiratory disease Within a strain there can be remarkable differences among sire families in susceptibility These facts show that heredity plays an important role in determining whether a bird will withstand disease or succumb to it.

To the best of the author s knowledge, no one has yet tried to breed a strain of fowls resistant to any one of these respiratory diseases. Strains of fowls resistant to lymphomatosis have however been developed by selection, and there are good indications that the same process would be effective against other diseases.

Real animals Some of the best demonstrations of the feasibility of breeding disease resistant animals have been made with the common house mouse. Unfortunately some of my students find it difficult to consider the mouse as anything more important than a geneticist s plaything To be sure it is better than a fruit fly but the question still remains Is it feasible to breed disease-resistant strains among the *real* animals? As all veterinary students know the real animals

are dogs and cats and anything bigger Hens qualify but just barely

It is the purpose of this book to review some of the evidence showing that domestic animals vary in genetic susceptibility to disease. Much of that evidence points the way to effective control of some diseases by the development of genetically resistant stock. It is *not* the purpose of this book to suggest that genetic control of disease is the only method of control or even the best way or that it should supplant other methods now effective and satisfactory In some cases it may be the best way· in others it may be entirely impractical. For at least one disease (lymphomatosis in the fowl) both genetic control and other methods can be effectively combined, and there are probably other cases to which the same applies.

Disease resistant plants Before proceeding further with domestic animals, perhaps we should see a little of what plant pathologists and plant breeders have done in the way of developing disease resistant varieties of important cultivated plants. Varieties of wheat resistant to stem rust provide good examples. As that disease spread over the spring wheat areas of the United States and Canada, varieties of wheat once reliable became economically undesirable because of their susceptibility Through the co-operative research of plant pathologists and plant breeders, new varieties were developed that combined resistance to most forms of stem rust with other essential qualities like high yield stiff straw and good milling and baking qualities. Dr R. F Peterson (5) of the Canadian Cereal Breeding Laboratory at Winnipeg has kindly provided the following brief history of that work

Basic rust-resistant breeding stocks of bread wheat were developed in the U.S.A. by transferring genes for rust resistance from other

species to bread wheats. Thus Marquillo and related varieties were developed from crosses of bread wheat with durum wheat, while Hope and sister strains resulted from crosses with emmer wheat. Further crosses with this basic material resulted in such outstanding varieties as Thatcher Rival and Mida in the U.S.A., and Renown Regent and Redman in Canada.

As new biological races of the rust fungus arose from time to time new genes for resistance had to be discovered to combat them. Race 15B with its ability to infect all commercial varieties, was a threat during the 1940's and became a serious problem in 1950. However such new varieties as Selkirk, developed in Canada, and Conley produced in the U.S.A. have given adequate resistance to this race. Even before these varieties were released, however hitherto unknown rust races were discovered to which the new wheats were susceptible. Other varieties now under test are resistant to all races known in North America. While the examples here given are from the spring wheat area of U.S.A. and Canada many other countries and regions have protected their wheat crops from rust attacks by breeding resistant varieties.

It is probably safe to say that had the plant breeders not developed varieties of wheat resistant to stem rust, there would be in North America today neither a wheat surplus nor cheap bread

In other crops other fungi cause rusts, blights, mildews, wilts and leaf spots. A list of varieties of grains vegetables, and fruits genetically resistant to these ineradicable pathogens would cover many pages One can hardly pick up a farm magazine without reading of some new oat resistant to crown rust, a strawberry resistant to yellows, a bean resistant to anthracnose or some disease resistant variety in other plants. Some varieties once resistant lose that valuable property when new forms of pathogens arise by mutation. In such cases new varieties must be developed to resist the new agent of disease.

On the other hand, some varieties have retained their original resistance for many years. A good example is the Martha Washington asparagus developed about 1912 for its resistance to rust, which soon became the most important variety in the United States and still retains that distinction. Varieties of cabbage bred at the University of Wisconsin for resistance to yellows have made it possible to produce that crop in areas where other cabbages could scarcely be grown. Similarly the Congo watermelon and other varieties resistant to anthracnose have quickly replaced the susceptible kinds grown earlier in the southeastern states. Tomato growing in southern states where fusarium wilt is a serious menace would scarcely have been feasible without the use of comparatively resistant varieties like Rutgers, Marglobe and others.

Many diseases of plants and animals are caused by viruses A good example of the utilization of genetic resistance to permit an industry to live with a virus, and to flourish in spite of it is provided by the cane-sugar industry in Louisiana A mosaic disease of cane proved fatal to practically all the noble varieties of the species of cane (*Saccharum officinarum*) used for the commercial production of sugar A single variety Wit Ceram was fairly resistant. Wild sugar cane (*Saccharum spontaneum*) is practically immune to mosaic but is not grown commercially because of its low yield of sugar

By crossing Wit Ceram with the wild species and repeatedly backcrossing the F_1 hybrids and their descendants to *S officinarum* a process called nobilization a cane can be produced of the desired noble type that carries also the all important resistance to mosaic. Interspecific hybrids thus

I am indebted to Dr H M Munger for information bout these disease-resistant egetables and fruits.

produced have now displaced the susceptible noble varieties and the cane sugar industry has if not an assured future, at least a reprieve until stricken by some other disease.

Other examples could be given of cultivated plants re sistant to virus diseases, but this book must give more space to animals than to plants Reviews of genetic resistance to plant diseases are given by Hayes *et al* (2) and by Walker (6)

Plants resistant to insects Insects are animals. Some of them feed on plants and some feed on other animals Many act as vectors carrying disease from plant to plant or from one animal to another Plant breeders have made remarkable progress in developing varieties resistant to insects (and to other animal parasites, including even nematode worms) but as yet animal breeders can show few similar achieve ments, if any The grape phylloxeran a plant louse that ravaged the vineyards for years was finally overcome by the discovery of resistant varieties some of which are said to have maintained their resistance for over ,o years. Pawnee wheat combines resistance to the Hessian fly with other de sirable traits of economic value Some varieties of maize are resistant to the chinch bug· others are completely destroyed by it. Details of these and other examples of genetic resistance to insects are given by Hayes *et al.* (2) and by Painter (4)

Some contrasts An important point to remember is that the development of all these disease resistant cultivated plants (and of many others too numerous to list) has resulted from recognition of these simple facts

1 The pathogen be it a virus a fungus, a bacterium or an insect, is not likely to be eradicated.
2 Within a species (or genus) some plants are generally able to live with the pathogen while others are not

5 By multiplying the good genes of the resistant individual plants one can obtain disease-resistant strains or varieties.

Unfortunately the views of those responsible for controlling disease in domestic animals [1] are almost diametrically opposite to those of the plant pathologists and plant breeders. The latter utilize every last bit of useful genetic variation in the host species to develop varieties that can tolerate the disease. In many cases that tolerance is aided by fungicides or insecticides that reduce the severity of infection. The veterinarians, on the other hand, concentrate all their attention on efforts to eradicate the pathogen or to reduce its frequency to a low level and (thus far) they have made little or no use of genetic differences among animals in ability to live with organisms that cannot be eradicated. When eradication proves futile, when carbolic acid and antibiotics fail to do their respective duties, protective vaccines are often invoked. These protect not only the biologically unfit that need them, but also the genetically superior animals that do not. And in all too many cases, the whole lot is slaughtered, including the genetically resistant animals, in the hope of thus preventing some other flock or herd from becoming infected.

The extent to which genetic resistance to disease has been utilized in the production of cultivated crops is well illustrated by Walker's review (6) of disease resistance in 19 common vegetables. For all but one of 74 diseases besetting these plants, genetic resistance has been demonstrated, and in 52 cases, at least, the diseases are controlled either completely or in part, by the use of varieties that combine genetic resistance with yield and other desirable traits of economic

[1] Excluding a few heretical geneticists and at least two veterinarians, of whom more anon.

importance. By the time these words appear in print, the list of resistant varieties will undoubtedly be much longer!

In striking contrast is the small number of cases in which genetic resistance has been deliberately utilized for the development of breeds or strains of domestic animals that are both productive and resistant to some specific disease To the best of my knowledge these cases can be counted on the *fingers of one hand. They are considered in detail in later* chapters.

The lack of progress and of interest in this field is indicated by the fact that in most currently authoritative texts on the general theme of animal breeding the subject of disease resistance receives only scanty attention or none Exceptions to that rule occurred in recent monographs on breeding dairy cattle by Gilmore (1) and on genetics of the fowl by Hutt (3) both of which devote a chapter to disease resistance In two leading texts on animal breeding the subject is not even listed in the index. A third, more hopeful in that respect, states simply that resistance to wilt is known in Indian melons!

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2 Hayes, H K. F R. Immer and D C. Smith. Methods of Plant Breeding 2d ed New York. McGraw Hill, 1955.
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Chapter II

Innate Disease

PERHAPS the simplest possible demonstrations that some animals are genetically resistant to disease and others genetically susceptible are afforded by comparisons of normal specimens with those that show at birth, or soon thereafter some genetic abnormality of form or function. Scores of such cases are known in domestic animals, and literally hundreds in man. Some of these congenital defects are so extreme that they cause the death of the afflicted animal before birth Others are lethal soon after birth or cause death at much later ages. Still others are not necessarily lethal but impose physiological deficiencies that necessitate special care and that may prove to be lethal in some environments.

In most of these cases the abnormal individual is homozygous with respect to some recessive gene. In other words, each parent has transmitted to the afflicted offspring a mutant gene that interferes with normal development. The double dose of that gene may disrupt the course of normal development sufficiently to cause death of the fetus or to induce some abnormality recognizable at birth. In such cases we may say that a calf is a "bulldog" or a hairless calf, that a lamb has "staggers" that a chick has "congenital loco" or is a

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late in fetal development with gross abnormalities of the buccal cavity

The protection afforded by a dominant allele against the pathogenic tendencies of its recessive partner may be more obvious if we take as an example some hereditary deviation from normal physiology Phenylketonuria will do nicely This is a simple, recessive autosomal abnormality of protein me tabolism in man. The homozygous recessive individual ex cretes unusually high amounts of phenylpyruvic acid and is either an idiot or an imbecile Clearly he is diseased. The heterozygote who carries only a single recessive gene for phenylketonuria is automatically protected against that disease by the dominant gene for normal metabolism and is apparently normal in all respects

It is not feasible to give a detailed list of lethal genes and physiological deficiencies here, so we shall have to confine ourselves to a few examples that will illustrate the kinds of disease against which most animals are protected by their complement of genes for normal development.

Achondroplasia About a quarter of the calves from pure short legged Dexter parents show an extreme type of achon droplasia and are commonly known as bulldog calves. Genetic studies have shown that these abnormal calves are homozygous for a dominant gene which in single dose causes only the shortening of the legs and the other characteristics that distinguish Dexters from other breeds of cattle The heterozygous Dexters are small in size and are considered particularly suitable for small farms. They are good milkers, and, apart from the shortening of the legs, it is debatable whether or not they should be classified as abnormal. The question of what is normal and what is not is a familiar topic *for debate, but one into which we cannot pry at this time.* Suffice it to say that the Dexters provide one of the cases

were absent but that the shoulder girdle and the pelvic girdle were normal or nearly so The acetabulum was represented merely by a knob.

This remarkable abnormality proved to be a simple recessive autosomal character The circumstances in which it appeared were rather unusual. Two breeders of Poland China pigs in Iowa had each bought purebred boars from the same source, and after the first breeding season the two boars were exchanged to avoid inbreeding From the resultant mating of each boar with the daughters of the other the ratio of normal to legless pigs was 207 25 If both sires were heterozygous for a recessive mutation that tends to induce the legless condition it was to be expected that half their daughters (from normal sows) would also be heterozygous. Accordingly from these matings the expectation was a 7 1 ratio or 203 29 The close fit of observed to expected numbers shows clearly that a recessive autosomal mutation was responsible. Apart from the unfortunate 25 pigs afflicted with these gross abnormalities, approximately two-thirds of the 207 normal litter mates could be expected to carry the gene for leglessness. The remaining third should have been homozygous for the normal gene.

Short spined cattle Another remarkable abnormality of the skeleton was studied in Oplandske cattle in Norway by Mohr and Wriedt (12) Affected calves had a shortened vertebral column They had practically no neck, and dissection showed the vertebrae to be so jammed together that of seven cervical vertebrae only the atlas appeared to be normal. Of thirteen thoracic vertebrae only five were recognizable. These short spined calves were mostly stillborn at full term but one or two were dropped alive and these died within a day or two

This abnormality was caused by a single recessive gene in the homozygous state. A remarkable thing about the action

of that gene is that its havoc was wrought entirely on the axial skeleton the limbs were normal As a result the calves appeared to have unusually long legs and were called elk calves by the farmers of the district, some of whom thought that they had resulted from matings of their cows with the wild elk of the district.

A similar short-spined condition has been found in tur keys. It is lethal in that species also



Figure Epithelial defects on the knees nd bov the hooves in all legs of an Ayrshire calf (From Hutt and Frost in *Journal of H red ty* 948.)

Epithelial defects in cattle Calves lacking more or less of the normal skin covering of the body have been reported in Holstein Friesians in Jerseys, and in Ayrshires. It is not clear that the same recessive gene is responsible for the abnormali ties in all three breeds. In the Ayrshires (Fig 2) small areas

devoid of the normal covering occur above the hooves of all four feet and also on the knees. There are raw areas on the inside of the ears, some lesions around the muzzle, and a narrow strip devoid of the normal epithelial covering in the roof of the pharynx and down the esophagus (Hutt and Frost, 5) In spite of these abnormalities the affected calves do not die soon after birth The one shown in Fig 2 was kept alive for several months others were sold for veal

By contrast epithelial defects in Jerseys are much more extreme The calves usually die before full term and are aborted showing large areas on the head and body devoid of normal covering In Holstein Friesians the abnormalities are less severe than in Jerseys but much worse than in Ayrshires The raw areas are more extensive than those shown in Fig. 2 and sometimes the abnormalities cause deformity of the ear The lesions become infected, and the calves die of septicemia usually within 3 weeks.

Those who find it difficult to consider congenital abnormalities as diseases might ponder this case. If the lesions themselves do not constitute a disease, at least the septicemia that results from bacterial invasion of those lesions is a disease In either case the calves homozygous for the causative recessive gene are susceptible to disease while their normal parents, though carrying that causative gene, are resistant to disease because of the protecting normal allele that they also carry

Hairless calves and naked chicks Most so-called hairless calves are not really completely without hair they usually have some hair at the end of the tail on the muzzle on the eyelids, and occasionally on the forelegs and in other parts of the body Mohr and Wriedt (11) studied in Swedish Holsteins a kind of hairlessness that was lethal in every case Apart from an almost complete absence of hair the affected calves

seemed to be normal. They were born alive at full term but all died within a few minutes of birth.

This recessive mutation was introduced to Sweden in 1902 being carried by an outstanding sire, Prins Adolph, imported from Germany. As often happens with imported sires, his descendants were greatly in demand for breeding, and, as a result, the undesirable recessive gene that Prins Adolph carried was widely distributed in Swedish Holsteins within 25

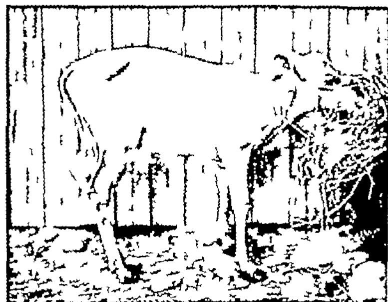
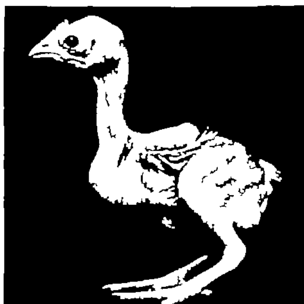


Figure 3. Recessive hairlessness, not lethal, in a Guernsey calf. (From Hutt and Saunders in *Journal of Heredity*, 1953.)

years. The same condition was later reported in Germany in stock related to Prins Adolph, and a similar lethal hairlessness, possibly the same mutation, was found in native cattle in Japan.

That hairlessness in cattle is not necessarily lethal was demonstrated by the Guernsey calf shown in Fig. 3. It was one of two sired by the same bull mated to related cows. Its

hairlessness was almost as complete as that associated with the lethal type and this apparently resulted from homozygosity for a simple recessive gene but it was *not* lethal (Hutt and Saunders, 7) At 8 weeks of age the calf shown in Fig 3 was almost completely devoid of hair except for the distal third of its tail and the insides of its ears. It was born on a cold January day and was protected with a blanket and some



F gu e 4 Sex-li ked, recessive nakedness i a cl ick of 3 weeks. A singl gene protects normal birds against this semilethal condition. (By permission, from *Genetic f the Fowl* by F B Hutt. Copyright, 949- McGraw-Hill Book Company Inc.)

extra heat from an infra red lamp during its first few weeks of life After 2 months it needed no special treatment and was raised to maturity It grew well but care had to be taken to enable it to avoid sunburn when it was turned outdoors in spring and summer

Hairlessness is known in rabbits, mice rats, and other mam

mals. The chick shown in Fig 4 was hatched with hardly a trace of the down that normally covers chicks at hatching. In this case the abnormality was caused by a recessive sex linked gene (4) and the first naked chicks were all females. It is a partially lethal character About 50 to 60 per cent of the females that carry the causative gene in their single sex chromosome die during the last 3 days of incubation Among those that hatch mortality is abnormally high unless they are brooded at about 100 F instead of the usual 90 F at which normal chicks are started. Those that survive develop more feathers in later life than they show as chicks. Although some of these survivors lay fairly well and reproduce nor mally it is clear that the mutation is one that could never sur vive in nature.

Muscle contracture An abnormality that has been found in cattle, sheep and swine is caused by varying degrees of muscle contractures. The limbs are bent and the joints firmly anky losed. Nine calves showing these extreme abnormalities were sired by one bull at an agricultural school in Norway (Tuff, 16) Several of them were born alive at full term but all had to be destroyed. Pedigree studies showed that all the cows that produced such calves could be traced back to a common ancestor The condition is clearly recessive and autosomal

Muscle contractures somewhat less extreme have been re ported in Holstein Friesian cattle in this country five such cases being found in one herd when a sire was mated with some of his own daughters and other relatives.

Studies of a similar but less extreme abnormality in sheep showed it to be caused by a recessive autosomal gene in the homozygous state. In both cattle and sheep birth of the young animal with rigid joints is often difficult and sometim es fatal to the mother A similar type of contracture has been studied in swine, but in that species usually only the front limbs are

involved. The affected pigs are usually born dead, and those alive do not survive more than 2 hours

Diseases of the nervous system Hereditary diseases of the nervous system are common in domestic animals as in man A good example is provided by an autosomal recessive mutation in Red Danish cattle. The affected calves have incomplete paralysis of the hind legs. They can rise to the knees but are rarely able to stand on the front legs. The hind legs are usually stretched out and if an attempt is made to bend them the calf extends the legs sometimes with a vigorous kick. These paralyzed calves are otherwise normal at first, but complications set in and death usually ensues within a few weeks

The study of this mutation by Nielsen (15) is probably the most extensive yet made of any lethal character in domestic animals. At least 347 paralyzed calves were recorded All of these for which pedigrees were known traced back to a bull Tjalfe Kristoffer born in 1913 By 1942 to 1946 the proportion of bulls known to carry the mutation was as high as 14 per cent of all bulls registered or exhibited at fairs with progeny The actual frequency of heterozygous sires in the breed was probably still higher From matings of carrier bulls with daughters of carrier bulls, either their own or those from other sires a ratio of 1,634 normal to 234 paralyzed calves resulted. This is almost exactly the 7 1 ratio that would be expected if the abnormality were caused by a simple recessive autosomal gene

Other hereditary diseases of the nervous system in domestic animals include cortical cerebellar atrophy of sheep, which has been reported in Welsh Mountain sheep in Border Leicesters, and in Corriedales.

Gregory *et al.* (5) have described a peculiar nervous disorder "congenital spasms which is lethal in Jerseys The

affected calves show intermittent spasms of the head and neck chiefly in a vertical plane. The calves do not like to stand because of spasmodic movements in all the legs. This simple recessive character proved fatal to all the affected calves within a few weeks of birth.

Similar diseases of the nervous system are known in the domestic fowl. The chicks shown in Fig 5 have a condition



Figure 5 Newly hatched chicks shown g congenital "loco recessive, lethal disorder (From Hutt I *Corn U F ten an* 934)

which pending some more accurate designation has been called congenital loco Because the affected birds cannot feed and drink it is usually fatal After being hatched the loco chick, when placed on its legs, will point the head upward over the back and eventually topple over to lie on its side or its back with the feet in the air Like so many other defects this is a simple recessive character

Hemophilia. This disease is known in man and in the dog, and in both species it is caused by a recessive sex linked gene. Because of some abnormality that prevents normal clotting of

the blood, the handicap is a severe one for affected animals, and only by giving hemophilic puppies transfusions has it proved possible to raise them to maturity The first symptoms shown by hemophilic pups, usually at 6 weeks to 3 months of age are lameness, large subcutaneous swellings and eventu-



Figure 6 Hemophilic puppy showing large swelling in the shoulder region caused by internal hemorrhage The skin was shaved after its death. (From Hutt *et al.* in *Journal of Heredity* 1948.)

ally paralysis of one or more limbs. The lameness is caused by bleeding into the joints, where the large masses of blood make any movement of the limbs very painful (Fig 6) Minor injuries sustained in normal play which would cause only a temporary bruise in most dogs can prove fatal to these hemo-

philic pups. One of them bled profusely from the gum following the eruption of a tooth. The hemorrhage could not be stopped by ordinary hemostatic agents, and eventually the dog had to be destroyed. Another ruptured a blood vessel supplying a limb when picked up by the owner and that hemorrhage proved fatal. Laboratory tests with the blood of four hemophilic dogs showed clotting times ranging from 11 to 40 minutes, whereas in normal dogs clotting time varied only from 1.8 to 6.5 minutes. In eight litters from heterozygous females, there were 32 females all normal, 23 normal males and 17 males with hemophilia. The disease is clearly caused by a sex linked recessive gene (Hutt *et al.* 1948).

This case provides an excellent example of the fact that the normal allele of a deleterious recessive gene provides resistance against the disease that would otherwise be caused by that recessive gene. Females that carry the gene for hemophilia in the heterozygous state are perfectly normal in all respects. Thus far it has not been possible even to devise a laboratory test that will identify such carriers.

If the mutant, sex linked gene for hemophilia is designated as *h*, its normal allele is *H*. With two sex chromosomes in females but only one in males, the following genotypes and phenotypes result from the usual mating of a heterozygous female (X_HX_h) with a normal male (X_HY). They occur in approximately equal numbers except for the slight excess of males that is normal in dogs.

Genotype		*Phenotype*
X_HX_H	♀	normal
X_HX_h	♀	normal, but a carrier
X_HY	♂	normal
X_hY	♂	hemophilic

It is clear that a single mutant gene induces typical hemophilia in males whereas the same dose is completely without

effect, so far as is yet known in females The latter are made disease resistant by the one *H* gene that the heterozygotes carry

They do not escape it just because they are females, for Brinkhous and Graham (1) have shown that it is possible to produce hemophilic females. This they did by using blood transfusions to rear hemophilic males to maturity and mating those males with heterozygous females. From these matings ($X_hY \times X_HX_h$) about half the puppies of each sex were hemophilic, as was to be expected. The hemophilic females thus produced did not show that disease because they had two doses of the causative gene but rather because they had no protection against a single gene They lacked the disease resistance that is provided by the gene *H* Most cases of genetic resistance to disease are more complex.

Lethal gray in sheep In sheep of various gray breeds (Sokul Shiraz Trourcana, and Karaculs) there is a remarkable hereditary abnormality of the digestive tract that is associated with the gray color characteristic of these breeds. When grays are mated together about a quarter of the progeny are black. Black is thus recessive, and most of the gray animals that reproduce are heterozygous for the two colors. Twenty-five per cent of the lambs from such gray parents should be homozygous gray There is good evidence from the studies of Nel and Louw (14) and others that about 75 per cent of these homozygous grays die within 9 months of birth They are subject to chronic bloating become emaciated and finally die Autopsies show impaction of the abomasum and other abnormalities of the digestive tract Apparently the troubles of the homozygous gray lamb are aggravated when it is weaned and switched over to the consumption of roughage. Nel and Louw recommend that lambs which can be identi

fied at birth as homozygous grays be destroyed to avoid subsequent loss. They are whiter in the coat than the heterozygous grays and usually have white tongues.

This case provides an interesting example, not only of a hereditary disease of the digestive tract, but also of a reduction in viability associated with a certain color. Whether that association results from the separate action of two closely linked genes one affecting color and the other the functioning of the digestive tract, or from the action of some one gene affecting both characteristics remains to be determined.

Fatal colors Lethal gray in sheep is one of several interesting cases in domestic animals in which homozygosity for some color or pattern is either fatal or a serious disadvantage. The first case of this kind found in animals was the now-celebrated yellow mouse. In 1905 the French zoologist Cuenot, reported that when yellow mice were bred together they produced approximately two yellow offspring to one not yellow. At a time when biologists everywhere were looking for three to one Mendelian ratios, this aberrant behavior called for further study. Eventually it was found that all yellow mice are heterozygous and that the homozygous yellows die at a very early stage in gestation.

The surviving yellow heterozygotes have several interesting characteristics. Apart from their unusual color they are somewhat more obese than their non yellow litter mates. This indicates that their rate of metabolism is probably different from that of the black mice. The yellows are also slightly bigger in the skeleton and peculiarly enough, are more resistant to mammary carcinoma than are their non yellow sisters. It seems most likely that the gene which converts black pigment to yellow also causes other profound changes in the mouse's physiology. In double dose the gene upsets

normal operations to such an extent that the homozygotes cannot survive even to late stages of gestation

An interesting parallel case is found in the platinum fox. This differs from standard silver foxes in having the black pigment greatly diluted throughout the pelt and the white areas increased There are a white snout and a white blaze up the face joining with a white collar When fox furs were in great demand the platinums commanded higher prices than the standard silvers Unfortunately platinum foxes cannot breed true When mated together they produce platinum and silver in the ratio of 2 1 and there is a corresponding reduction of litter size by about 25 per cent. Conclusive evidence has shown that homozygosity for the platinum color is fatal but it is not yet definitely established whether death occurs early in gestation or at birth The same applies to another kind of deviant from the standard silver one which is called white faced or white marked silver In both cases as Johansson (8) has shown not only is the mutation lethal to the homozygote but it also lowers somewhat the viability and reproductive efficiency of the heterozygous platinum and white faced silver foxes.

Though the minks have won out, at least for the present over the foxes in popularity in the fur market they are not exempt from some of these fatal colors There is good evidence that the silver sable or Blufrost mink is always heterozygous and that the homozygotes perish early in gestation The Blufrost mink differs from the dark wild type in having the pigment reduced in the guard hairs and in the underfur As a result, some of the guard hairs appear silvery and the underfur is light blue.

With all the fatal colors mentioned above the causative gene is dominant to the normal condition or what the geneticist calls the "wild type Some of the heterozygotes show

traces of the fatal disease that kills their homozygous siblings, but most of them are viable and normal, or almost so. In these cases the resistance of the heterozygote to the pathological condition afflicting the homozygote depends upon its having only a single dose of the damaging gene rather than two When matched against its recessive allele, the adverse influence of the dominant gene is offset by the efforts of its recessive allele to induce normal development. It is not stretching things too much to say that resistance to disease is provided in such cases by the recessive allele.

Frequencies Let no reader suppose that the few examples cited in this chapter are the only cases of innate disease known in domestic animals. To review all such defects in domestic animals would necessitate writing another book. The examples have been chosen to illustrate the fact that congenital disease caused by a single gene in the homozygous state can affect the skeleton the integument the nervous system, the muscles and the functioning of the blood or of the digestive tract. Even the color of the coat, which is sometimes considered an unimportant superficial character can be an indicator of some unhealthy state inside it.

Some idea of the frequency of such abnormalities can be obtained from recent reviews. In Swedish cattle Larsson (10) found 10 lethal characters and 10 other defects that each seemed to be caused by a single pair of genes. Similarly in Holland, Gotink *et al* (2) listed 9 lethal characters and 31 other hereditary defects known to have occurred in cattle of that country alone Six bulls of dairy breeds taken at random and tested by Mead and Gregory (13) were found to carry 2 lethal characters and genes for 6 other simple defects. In 1949 Hutt (4) listed 21 lethal genes known in the domestic fowl and a number of others have since been identified

From such surveys and from genetic studies in other spe cies it seems probable that most animals carry a certain amount of what one geneticist calls genetic junk. One won ders how long it may be before some sire that has fathered several hundred calves through a center for artificial insemi nation will be found to have disseminated some undesirable genes as well as his good ones

Elimination of recessive defects Lethal genes and defects like those considered in this chapter can be eliminated from a flock or herd even in large domestic animals. Suspected heterozygotes should be tested before being used extensively for breeding Obviously such tests are particularly important with sires, since one male will distribute a bad gene to many more offspring than can any one female.

The best test is to mate the suspect to known heterozygotes, i e to any females that have produced the undesirable trait. A single affected offspring from such matings is enough to show that both its sire and dam are heterozygous. If the suspected sire is mated with females known to be heterozy gous for a simple recessive defect 8 progeny if all normal will reduce to 10 per cent the probability that the sire could still be carrying the unwanted gene. Each normal offspring above that number reduces the probability still more If there are as many as 12 normal progeny with none showing the trait for which the test is made the chance of that sire s carry ing the unwanted gene is reduced to 5 per cent.

In another type of test mating, in which the suspected sire is mated with his own daughters or with daughters of some other sire known to be heterozygous for the defect, the ex pected frequency if he is heterozygous, is 7 normal to 1 de fective. Such a test is more difficult than the other for at least 17 progeny all normal are needed to reduce to 10 per

cent the probability that the sire is not carrying the unwanted gene.

Some recessive defects are not completely recessive. In such cases careful study may provide some test or measure by which heterozygotes can be identified, thus making genetic tests un necessary A good example, currently of much interest to those who raise Aberdeen Angus or Hereford cattle is provided by the unthrifty dwarf calves that occur in these breeds (in North America) with an alarming frequency If the animals that carry the unwanted gene could be eliminated from the breeding herd, the problem could easily be solved. To that end geneticists are now measuring the conformation of the head and deviations in certain vertebrae in the hope of finding some method of identifying the cattle that are heterozygous

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Chapter III

On Coping with the Environment

IN the previous chapter we considered a few examples of disease that results from variations in the genetic constitution of animals. All of the conditions there described are recognizable at birth or soon thereafter because of some visible abnormality of the anatomy physiology or color of the animal affected Fortunately congenital defects like those considered in Chapter II are exceptions and most animals are born in what appears to be a perfectly normal condition. However when these apparently normal newcomers to this earth face the varying kinds of environment with which they must cope during their stay upon it it soon becomes evident that some can tolerate that environment better than others. As we shall see these differences in ability to cope with the world around us result in large measure from differences among us in our genetical equipment for that task. Usually it takes some particular kind of environment to reveal those genetic differences and in the most favorable conditions many of them may never be brought to light.

In this chapter we shall consider a few examples to illustrate how the genotype can interact with the environment to

determine the ultimate fate of the animal. Environmental influences are not always obvious. Most people think of the environment as being represented by such things as heat, cold, drought variations in the amount of light and other physical factors However it includes also the quality and quantity of food available and the pathogenic organisms and parasites to which an animal may be exposed. Other wearing environmental influences are sometimes less obvious such as competition among animals particularly among wild ones, and assorted lesser irritants like income taxes and poison ivy

In some cases the environment has no effect whatever in others it appears to be the all important factor in determining some condition. Often it is difficult to say which exerts the most influence—heredity or environment—and many a debate on that subject has left the matter undecided Geneticists recognize that the environment may be an all important factor in determining the expression of some genetic character The purpose of this chapter is to give a few examples that illustrate various kinds of interactions between heredity and environment particularly those that are related to disease

Genetic differences in toleration of hot weather Cattle of the Zebu type so common in Asia and Africa are now being used in various parts of the world to produce new breeds that combine useful productivity with superior ability to tolerate high temperatures. The remarkable abilities of the Zebus to retain their bovine complacency (Fig 7) when high temperatures have completely upset cattle of European origin is well illustrated by some tests made by Rhoad (14) with pure Zebus pure Holstein-Friesians, and eight F_1 animals from the cross between those two breeds. When air temperatures got as high as 97 F., the Holstein Friesians were panting at the rate of 107 respirations per minute The corresponding rate for the



Figure 7 Brahman cattle basking the sun while European breeds seek shade. (Courtesy American Brahman Breeders Association.)

Zebus was only 46 while that of the F animals was intermediate at 89 (Fig 8)

Recognition of this remarkable ability of the Zebus to withstand high temperatures led to their use at the King ranch in Texas to form the famous Santa Gertrudis breed, which is about three-eighths Zebu and five-eighths Shorthorn. From their home base the Santa Gertrudis have gone to hot climates farther south, to Queensland, and to other parts of the world in all of which they have invariably given an excellent account of themselves as beef animals.

In Jamaica Zebus of the Sahiwal breed have been crossed with Holsteins to produce the Hope Holsteins, a dairy breed with ability to yield more milk in tropical heat than can the pure Holsteins introduced from Europe. In these Hope Holsteins, according to Lecky (12) the best milkers have a little over 25 per cent of Zebu blood, and it is considered that the ideal would be about three-eighths Zebu In the Philippines

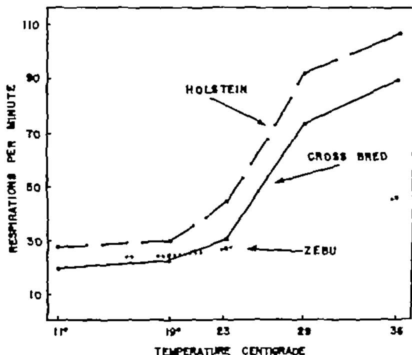


Figure 8 Respirations per minute at different air temperatures. (From Rhoad, in *Journal of Agricultural Science* 1936 by permission of Cambridge University Press.)

the Zebu has been crossed with Herefords to produce a beef draft animal adapted to that part of the world. Another cross being tried in the southern United States is the Charbray a combination of Zebu with the French Charollais.

In all these crosses the important contribution of the Zebu is its ability to thrive at high temperatures, but it is also more resistant than European cattle to tick-borne diseases. Both these desirable qualities are transmitted in good measure to its hybrid progeny The cross is of particular interest because it provides one of the few cases in which animals of two different species have been crossed to produce a superior hy

brid for man's use. The Zebu (*Bos indicus*) and European cattle (*Bos taurus*) both have thirty pairs of chromosomes, and crosses between them are fully fertile

Heat resistant Leghorns Many a poultryman has found by experience that Leghorns can withstand high temperatures better than can the heavy breeds This was nicely demonstrated at Cornell some years ago when our flocks were subjected for three July days in a row to temperatures unprecedented in the previous 11 years (Hutt, 9) During the whole heat spell of some 6 days mortality from heat prostration alone was as follows

	Birds number	*Died per cent*
White Leghorns	159	8
Rhode Island Reds	8	5.3
Barred Plymouth Rocks	6	5.2

In mortality from other causes before, during, and after the heat spell these three breeds did not differ significantly but deaths from heat prostration were three times as high in the two heavy breeds as in the Leghorns, and those differences were statistically significant.

Study of the records showed that resistance of the Leghorns to high temperatures was not related to their small body size Subsequently Fox (4) has given an interesting clue to the reason for Leghorn superiority in this respect. He found that when Leghorns and heavy breeds were exposed together to extremely high temperatures, they did not differ in ability to survive so long as both breeds were deprived of water However when the birds were given an opportunity to drink all they wished the White Leghorns drank more or less continuously and survived but the New Hampshires and Rhode

Island Reds drank less and perished. This indication that the Leghorns were either more thirsty or more intelligent, or both, was accidentally confirmed in one test when four of the five White Leghorns subjected to extreme heat broke out

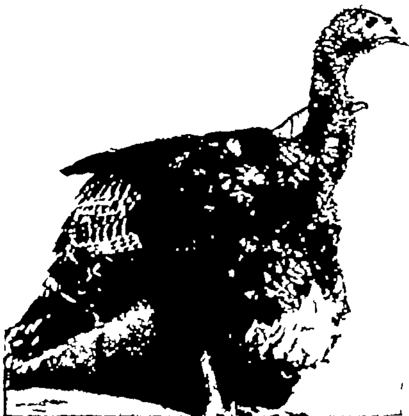


Figure 9. Pend lous crop, the result of combined genetic and environmental influences. (From Hinshaw nd Asmundson in *Journ l f America Veterinary M dic l Associat on* 93f)

of confinement and got to the water pan. None of the heavy breeds did so

Since ability to withstand high temperatures is as much a breed characteristic of the White Leghorns as are their white

color and single comb it is clearly a genetically determined trait. Fox's experiments suggest that the Leghorns may be genetically better endowed with the gumption necessary to cope with an extremely unfavorable environment.

Pendulous crop in turkeys At Davis, California Asmundson and Hinshaw (1) studied a remarkable abnormality in Bronze turkeys which they called pendulous crop In affected birds the crop becomes filled with fluid and greatly distended (Fig

Table 1 Relation of temperature to incidence of pendulous crop in genetically susceptible turkeys

Place	Maximum daily temperature, average	Highest temperature recorded	Poults exposed, number	Incidence of pendulous crop, per cent
Davis	92.5 F	09 F	67	67
Tomales	4 F	92 F	83	

From Asmundson and Hinshaw in *Poultry Science* 958.

9) About a third of them die sometimes from pneumonia or from self inflicted lacerations and subsequent septicemia, but all are unthrifty and most of the survivors cannot be mar keted Because the pendulous crops were found only in the Mammoth Bronze turkeys and never in the Bourbon Reds raised at the same place the condition was evidently a genetic character This was confirmed by selection for increased incidence of the abnormality which resulted in the development of a strain in which over two-thirds of the turkeys from afflicted parents developed pendulous crop.

It was noticed that this condition appeared in poults from 8 to 16 weeks of age after excessive drinking in hot weather To test further that environmental influence susceptible poults were divided in two groups and one sent from Davis to Tomales, which is only 2 miles from the ocean. The results of this experiment (Table 1), show clearly that in the cooler

atmosphere at Tomales the genetic susceptibility to pendulous crop was never expressed.

This case illustrates how some abnormality in one environment might appear to be caused entirely by heredity but in another to be induced solely by temperature or by some other extraneous factor

Disease and diet In an age when we are constantly exhorted to down our thiamine, vitamin C vitamin D and iodine so that we shall not develop beriberi scurvy rickets and goiter it is hardly necessary to remind the reader that dietary deficiencies can cause disease No text on the feeding of domestic animals is complete without its series of ghastly pictures to show what happens to rats, chicks and other animals that do not eat their vitamins and minerals. Less evident but none the less real are the effects of dietary deficiencies on performance and production. However there are genetic differences in ability to get along on deficient diets. Some of these interactions of heredity and environment will be discussed in later chapters but two or three examples can appropriately be mentioned here Heston (7) has described a hereditary abnormality in the rat in which the nose is bent to one side. It is manifested only when the calcium phosphorus ratio is unbalanced. In the bent nose strain about 50 per cent of the rats showed the condition on diets too high in calcium. However when cod liver oil was added to the diet the incidence dropped to 14 per cent, and when irradiated yeast was added only 4 per cent of the rats showed the bent nose. Similarly Gilman (5) studying hereditary brain hernia in swine found that sows on deficient diets produced herniated pigs with a frequency indicating the condition to be a simple recessive character When the same sows were fed a fully adequate diet, however the proportion of herniated pigs in their litters (by the same boar as before) was greatly reduced

Natural selection against inadequate diet Some years ago a nutritionist just returned from China stated that he could not see how the Chinese people managed to live with an intake of calcium as low as he had found it to be there One possible answer is that over thousands of years people unable to thrive on a somewhat lower level of calcium than the 0 8 grams daily that some authorities on nutrition prescribe for adults in North America would have been eliminated by natural selection Those best able to survive and to reproduce on a low



F gur An extreme case of perosis (Courtesy Cornell University)

calcium intake would eventually beget a race capable of similar performance

The fact that natural selection does operate in this way is illustrated by data from Hawaii on the incidence of slipped tendon or perosis (Fig 10) in different strains of chickens In this abnormality the tarsometatarsal joint becomes enlarged bones of the shank become curved and frequently the tendon from the gastrocnemious muscle slips from its intercondylar groove. Perosis results from a genetic susceptibility to an unbalanced diet.

Serfontein and Payne (16) found that when its frequency in Rhode Island Reds was 15 per cent their Leghorns on the same diet showed only 0.7 per cent affected. By selecting susceptible breeding stock from chicks that had shown perosis but had recovered, they were able to increase the incidence of the abnormality to 50 per cent in the next generation. Clearly chicks differ genetically in susceptibility to perosis. *On the other hand* the frequency can be reduced by providing in the diet some supplementary manganese. Chicks of the heavy breeds may need as much as 50 parts per million of manganese in their feed to reduce the incidence of perosis, but Leghorns seldom show it even when the manganese content is no more than 30 parts per million.

Rosenberg and Tanaka (15) imported into Hawaii three strains of New Hampshires from California, Washington, and Oregon. These were brought in as chicks and were compared in Honolulu with New Hampshires of a strain that had been bred in Hawaii for a number of years. All birds received the same diet, which contained ample manganese. By 12 weeks of age the incidence of perosis in the three introduced strains varied from 3.9 to 5.2 per cent but not one chicken of the Hawaiian strain showed that abnormaltiy. Now perosis is more likely to develop in chickens raised on wire mesh floors than in those on solid floors or on the ground. Because of the prevalence of parasites in Hawaii it is the usual practice there to raise all chickens on wire floors. It seems probable therefore that several years of natural selection had eliminated from the Hawaiian strain of New Hampshires most birds genetically susceptible to perosis. In the United States however few chickens are raised on wire floors in the three states from which the stock was imported. Any selection there against that disease must have been much less intense because the birds had not been raised

on wire. It is not surprising that when forced to cope with the wire floors conducive to the development of perosis the imported strains all showed some susceptible birds but the Hawaiian one did not.

This case shows nicely how genetic variation in susceptibility to a disease and an environment conducive to development of that disease together provide a situation in which natural selection operates to breed a resistant stock. However natural selection, like the mills of God, grinds slowly particularly with a species yielding only one generation a year A geneticist seeking to develop quickly a strain of New Hampshires highly resistant to perosis would require his chicks to cope not only with wire floors, but also with a suboptimal intake of manganese, in order to get the maximum expression of genetic susceptibility and resistance. With family selection and progeny tests he should then quickly outdistance the relatively slow process of mass selection through which nature operates.

Decayed teeth on coarse feed. An interesting example of the interaction of genetic and environmental influences is provided by the dental caries studied experimentally in rats by Hunt and Hoppert (8)

Contrary to what we have been told about our own teeth by eminent authorities, rats develop tooth decay more rapidly on coarsely ground feed than when the same diet is fed in a finely ground form This perverse and nonconformist behavior is disturbing Rather than lose any faith in the experts who guide us, we can subdue all incipient distrust simply by reminding ourselves that the rat is one kind of animal and man quite another What is good for a lowly rodent is not necessarily good for the most advanced species among the primates This philosophy is reassuring until we

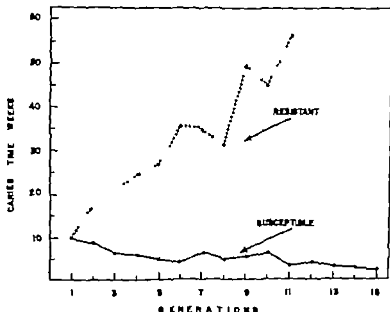
recall with dismay that in every laboratory of nutrition worthy of the name the rats outnumber the humans by scores to one and that both species collaborate to prescribe for us what vitamins and minerals we should eat and what more delectable items we should not

Using a diet so coarse that 70 per cent of its ground, hulled rice was retained by a 20-mesh screen Hunt and his associates measured the susceptibility of their rats to tooth decay by *caries time* *This was the number of days after being* put on the coarse feed before appearance of the first sign of decay Young rats were started on the caries-inducing diet at about 35 days of age For the unselected stock with which these experiments began the mean caries time was 70 days. By selective breeding two contrasting lines were differentiated one being highly susceptible to caries and the other remarkably resistant (Fig 11) In the eleventh generation the mean caries times in these two lines were 22 days and 392 days respectively As environmental conditions had been kept uniform for all rats tested, the difference between these two lines obviously resulted from selection. Clearly resistance to decay of the teeth depends in large measure on the genetic contribution of the rat

A simple test showed just as clearly that resistance also depends a great deal on at least one factor in the environment, i.e the coarseness or the fineness of the feed In the ninth generation the mean caries time for rats of the susceptible strain in routine tests was 30 days. However other rats of that same breeding were raised on feed ground as fine as flour but otherwise identical with that provided in the routine tests On that fine feed 53 rats showed not a trace of *decay even at 150 days of age, and for the remaining 4 animals* the mean caries time was 125 days.

If these fine and coarse feeds had been tested on rats of

unknown genetic constitution with respect to dental caries the investigator might well have concluded that the all-important factor causing tooth decay (in the rat, remember!) is coarse feed. On the other hand, the genes clearly exert a



Figur Differentiation by selection of lines of rats resistant or susceptible to dental caries. (Drawn from data of Hunt nd Hoppert in *Journ l of Dent l Research* 918.)

remarkable influence (Fig 11) The importance of both heredity and environment is clearly revealed by suitable experiments with genetically controlled material

Death delayed by wet feed In chickens a simple dominant mutation was found by Sturkie (17) to cause reduction of some of the feather tracts, thus leaving the chick partly naked Under normal conditions with dry feed Sturkie

found that 58 per cent of the mutant chicks died by 15 days of age. Peculiarly enough when the naked chicks were started on wet mash death was postponed, and mortality at 15 days of age was only 28 per cent. After wet mash was discontinued mortality again rose and by 150 days it was almost as high as in naked chicks on dry feed The naked chicks did not eat well on dry feed. By providing moist feed which is more attractive to chicks than the dry kind, they were induced to consume enough feed to meet the higher requirement of energy imposed by their partially naked condition.

The influence of natural selection was nicely demonstrated in this case After backcrossing heterozygous naked chicks to normal fowls for eight generations, the degree of nakedness was greatly reduced and viability was much increased (18) The proportion of chicks dead by 15 days in the eighth generation was only 9 per cent It seems probable that the continued backcrossing had resulted in the accumulation by the surviving chicks in each generation of modifying genes that reduced the degree of nakedness and permitted correspondingly better viability even on the dry feed.

Influences of light Proof of the old adage that one man's meat is another's poison is afforded by the varying effects of sunlight on different genotypes. Basking on the beach is a much safer pleasure for brunettes than for blondes A bad case of sunburn is really a condition of disease, and obviously the brunettes are much more resistant to it than their fair haired sisters Some domestic animals are genetically so photosensitive that when exposed to sunlight they become badly burned These will be discussed in a later chapter It will suffice here to point out that pigs or people afflicted with porphyria like the sheep that carry an excess of phylloerythrin in their blood, can get along very well so long as they keep out of the direct sunlight.

Another interesting effect of light, although not related specifically to disease is its influence on activities of the endocrine glands in birds. Late-hatched pullets are slow to begin laying but can be brought into profitable egg produc tion by exposing them at about 5 or 6 months of age to in creased amounts of light.

The chain of reactions here is an interesting one. Light received through the eye and passed along the optic nerve activates the anterior lobe of the pituitary gland. That gland then produces a gonadotropic hormone which activates the ovary and thus causes the pullet to lay Since in northern latitudes the length of the day decreases steadily after June 21 pullets that are hatched late in April and become somat ically mature in September are then subjected to shorter days than their March hatched sisters experienced when they were 5 months old. Thus the April birds are usually 2 or 3 weeks older at the first egg than are the pullets of early March when they start laying, unless artificial light is sup plied.

This effect of light on age at sexual maturity is nicely illustrated (Table 2) by two years data for unlighted pullets hatched early late or in mid-season at Cornell University

Table 2. Relation of date of hatching to age at first egg in White Leg horn pullets

Strain	Year	Mean age in days at first egg (a) Hatched March 5–	(b) Hatched March 24– April	(c) Hatched April –29	Difference (c–a), days
K	935	64	7	93	+30
K	934	6	70	177	+ 6
C	935	59	66	89	+30
C	9 4	55	69	70	+ 5

Data of Hutt nd Cole, Cornell U iversity

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Influences of light. Proof of the old adage that one man's meat is another's poison is afforded by the varying effects of sunlight on different genotypes. Basking on the beach is a much safer pleasure for brunettes than for blondes. A bad case of sunburn is really a condition of disease and obviously the brunettes are much more resistant to it than their fair haired sisters. Some domestic animals are genetically so photosensitive that when exposed to sunlight they become badly burned. These will be discussed in a later chapter. It will suffice here to point out that pigs or people afflicted with porphyria, like the sheep that carry an excess of phylloerythrin in their blood, can get along very well so long as they keep out of the direct sunlight.

Another interesting effect of light, although not related specifically to disease, is its influence on activities of the endocrine glands in birds. Late-hatched pullets are slow to begin laying but can be brought into profitable egg production by exposing them at about 5 or 6 months of age to increased amounts of light.

The chain of reactions here is an interesting one. Light received through the eye and passed along the optic nerve activates the anterior lobe of the pituitary gland. That gland then produces a gonadotropic hormone which activates the ovary and thus causes the pullet to lay. Since in northern latitudes the length of the day decreases steadily after June 21 pullets that are hatched late in April and become somatically mature in September are then subjected to shorter days than their March-hatched sisters experienced when they were 5 months old. Thus the April birds are usually 2 or 3 weeks older at the first egg than are the pullets of early March when they start laying unless artificial light is supplied.

This effect of light on age at sexual maturity is nicely illustrated (Table 2) by two years data for unlighted pullets hatched early late or in mid season at Cornell University

Table 2. Relation of date f hatching to age at first egg in White Leghorn pullets

Strain	Year	Mean age in days t first egg ( ) H tched March 5–	(b) Hatched March 24–April	(c) Hatched April –29	Difference (–a), days
K	953	64	7	94	+30
K	954	6	70	77	+ 6
C	953	59	66	89	+30
C	954	55	69	70	+ 5

Data of Hutt nd Cole Cornell University

The groups compared were all from the same hens in any one year The data show a genetic difference between Strains K and C, with the latter maturing approximately 5 days earlier than the former In 1951 the late-hatched pullets did not begin laying until they were some 2 weeks older than their early-hatched sisters had been when they began A difference between years is also evident for in 1953 the pullets hatched last were 30 days older before beginning to lay than those hatched earliest. Obviously some additional environmental factor retarded the late-hatched birds of 1953

Since age at first egg is a genetically determined character and one that can easily be modified in either direction by selection this case affords a good example of the interaction between heredity and environment.

Other interactions stress factors It is fashionable in some biological circles at the present time to refer to all adverse environmental conditions under the general heading of stress factors The latter term includes practically anything that tends to irritate the organism This might include too much sun or too little the things that cause common colds, an excess of alcohol or of blatant commercials on television

Various species have demonstrated remarkable ability to adapt themselves to stress factors. One need only recall the house flies that become resistant to DDT in an amazingly short time or the codling moths which in a much longer time have become resistant to arsenical sprays Perhaps the greatest degree of adaptability has been demonstrated by some of the bacteria that have had to cope with antibiotics. In *Escherichia coli* there are now not only strains resistant to penicillin but also strains that actually require that antibiotic for optimum growth The same can happen with path

ogenic organisms, as Barber (1) has demonstrated with *Staphylococcus aureus*

Adaptation of a species to its environment is not peculiar to insects and bacteria, but in larger forms with slower reproduction it is less evident. Examples in domestic animals are reviewed in later chapters. In man natural selection has done much in the first half-million years to build a resistant organism but in the last half-century thanks to the highly effective efforts of the medical profession to foil that process, adaptation has become in many parts of the world more of a problem *for the individual than for the species*. Here also the struggle is often between one's genes and the environment.

The situation is illustrated by a friend, a geneticist, whose stress factors include house dust, goose feathers, and kapok, all of which give him asthma, and the weekend traffic between San Francisco and Palo Alto on the Freeway which causes excessive perspiration. His allergies like most are hereditary but a genetic basis for his reaction to traffic has yet to be demonstrated. By using an immunizing extract of house dust, putting plastic covers on the pillows, taking an occasional whiff of adrenaline and shun-piking on weekends, he has managed for some 60 years to cope successfully with his environmental stress factors and, in spite of his genetic unfitness, to survive.

Somewhat similarly under favorable environmental conditions, most of us have beaten off the organisms causing chicken pox, measles and mumps as well as the bacteria that invade us every time we cut a finger. Over 99 per cent of us (adults) have withstood poliomyelitis without the protection of any vaccine.

If the environment is sufficiently adverse even the highest degree of genetic resistance to infection may be futile. Colin

tried for weeks to infect chickens with anthrax but failed in every attempt. Eventually Pasteur showed him that it could easily be done by immersing the birds in cold water and thus lowering their normally high body temperatures below the 105 to 108 F which ordinarily protects them against not only the anthrax bacillus but other bacteria as well

Heredity environment and the twin study method In species producing both monozygotic (identical) and dizygotic (unlike) twins a very precise technique can be used for determining whether or not some characteristic is caused more by heredity than by environment or vice versa. It is called the twin-study" method. Since monozygotic twins result from division of a fertilized egg both members of the pair should have the same genetic constitution except for any mutations than may have occurred after their separation. Accordingly if the trait under consideration is determined primarily by genetic susceptibility then when one twin shows it the other should do so also in most cases On the other hand dizygotic twins are no more alike than brothers and sisters born at separate times They may be of opposite sexes one may have brown eyes and the other blue. We should expect the concordance in such dissimilar twins to be no higher than that in siblings

Now if the trait being investigated is determined in large measure by environment and heredity has little or nothing to do with it, then the concordance within pairs of dizygotic twins (particularly in those of like sex) should be just as high as in monozygotic twins. If, on the other hand, heredity is the all important factor in expression of the trait, then concordance in the monozygotic twins should be much higher than in the dissimilar pairs

In such studies of twins to differentiate between the effects

of environment and heredity one must be careful to get a random sample of the twin population. Bias is introduced otherwise because pairs in which twins agree are more likely to be reported than pairs in which they do not.

Twins and tuberculosis Kallmann and Reisner (10) studied 308 pairs of human twins in which at least one member (designated as a "twin index case") developed tuberculosis The incidence of that disease was then determined in the other members of the pairs and in their full siblings and other relatives to a total number of 1 308 people. While the incidence of tuberculosis in the general population was only 1 37 per cent, the chances of that disease striking relatives of tuberculous twin index cases were found to be as follows

	Per cent
For full brothers and sisters, not twins	25.5
For dizygotic co-twins	25.6
For monozygotic co-twins	87 3

The fact that concordance was so high in monozygotic twins, but no higher in dizygotic twins than in siblings born separately shows clearly that susceptibility to tuberculosis in man is in large measure genetically determined This of course does not rule out an environmental effect as well. Obviously if a susceptible person never becomes infected, he cannot develop tuberculosis. Now that the incidence of tuberculosis in the general population has been reduced in North America to hitherto-unprecedented low levels, this is exactly what is happening to many genetically susceptible people. They are escaping the disease because they are never exposed.

It does not follow that among infected persons all are equally susceptible As Kallmann and Reisner point out, there

are all gradations from a high degree of genetic resistance to a very low one Between these extremes some people might develop mild tuberculosis and recover if the environment is favorable When the environment is not favorable then some of these intermediates might succumb as thousands of them did in Europe during the privations of the Second World War

Susceptibility to mycotic infection in cattle Both types of twins occur in cattle a fact which is now being utilized by investigators in Sweden New Zealand Scotland and the United States for more precise investigations in animal husbandry than are possible without twins. A pair of identical twins is about as close as we can come in large mammals to what the plant breeders call a pure line that is, one in which the individuals are genetically alike By using one twin calf as a control and subjecting its mate to the experimental diet, the reduced intake of feed, or whatever the investigator wishes to study the effect of the treatment is measured more exactly than is possible with heterogeneous material. Thus, for studying the factors influencing milk yield in cattle investigators in New Zealand have concluded that a pair of identical twins is as good as 22 cows that are not twins.

Apart from such studies in animal husbandry however the only case thus far reported in which twins have been utilized in domestic animals to demonstrate the separate influences of heredity and environment in causing disease comes from a single pair of twin heifers. At Wiad, Sweden where Bonnier and Hansson (6) have had twin calves under study for many years, one member of an identical pair became ill when nearly 35 months of age, deteriorated rapidly and died at 1 day over 35 months. Post-mortem examination showed that death was caused by an acute mycotic intestinal inflamma

tion. The mucous membrane of the intestines was infiltrated with molds (*Aspergillus* and *Mucor*), which were traced to moldy hay that had been fed to the animals.

Exactly 2 weeks after the one twin first showed symptoms, her mate began to exhibit exactly the same conditions and, as her condition deteriorated rapidly she was slaughtered just 2 weeks after the other had died On examination the same infiltration of molds in the mucous membrane of the intestines was evident.

Among 104 head of other cattle to which the same hay was fed, no unfavorable effects whatever could be noticed. It is clear that this one pair of identical twins differed from other cattle in being genetically highly susceptible to the molds in their hay If the stricken heifers had not been monozygotic twins, it could not have been discovered that resistance and susceptibility to such an infection are determined by heredity Identical twins in cattle are not common, however and in other species of domestic animals they are more difficult to identify if they occur at all.

Longevity About the most satisfactory measure of an animal's ability to withstand the cumulative action of all the environmental stress to which it may be subjected is its length of life. Unfortunately we do not know the average duration of life in domestic animals. To be sure, we read frequent reports of ancient horses and of hens that have continued to perform well long after the rest of their generation has departed. Although such records are interesting as indicators of the extremes of longevity in such species they are of little value as measures of the average expectation of life. For most domestic animals the duration of life is determined by their economic usefulness only

We can do somewhat better with man who is usually given

every possible opportunity to demonstrate how long his genes will let him live There is ample evidence that, except for those killed by bombs machine guns, automobiles or other infernal agencies the duration of life is determined by heredity From records of nearly 2 500 members of the Hyde family Alexander Graham Bell calculated that the chance of persons in it living to 80 was only 5.3 per cent if neither parent attained that age It increased to 9.8 per cent when one parent did so but for those whose parents both became octogenarians, the prospect of attaining that same distinction rose to 20.6 per cent.

Similarly from studies of the correlation in age at death between parents and offspring Beeton and Pearson concluded that one-half to three-quarters of the mortality rate is determined solely by heredity and is not likely to be influenced by measures of public health Since their studies were made in the ante-antibiotic era that conclusion might now stand some modification.

Evidence of the role of inheritance in determining longevity was obtained in a different way by the Pearls (13) They compared 365 people still living at 90 or beyond with a large number of suitable controls. For both groups they determined the sum total of the lengths of life of six immediate ancestors of each person (father mother and four grandparents) For the nonagenarians and centenarians, that figure was more than 60 years higher than it was for the controls. In other words, people over 90 came from immediate ancestors whose length of life was about 10 years longer per person than the corresponding ancestors of the controls

More recently Dublin and Marks (3) studied the records of all white men between the ages of 20 to 64 to whom policies were issued by the Metropolitan Life Insurance Company between the years 1899 to 1905. From these they excluded cases

with unusually youthful parents that might have biased the analysis and sorted the remainder into three groups according to whether both one, or neither parent of the policyholder had been living when the policy was issued. Within these groups the subsequent mortality was compared with the ex pected (average) mortality for males of the same age. Regardless of the age at issuance of the policy the ratio of actual mortality to that expected was consistently lowest for those whose parents were both still living, and highest for those who had neither parent living, when the policy was issued. Clearly there is a relation between duration of life in the parents and that in the offspring.

As with the study of other genetic characters, twins are useful for demonstrating the relation of heredity to duration of life. If there were no such relation then monozygotic twins would be no more likely to die at about the same age than would dizygotic twins However Kallmann and Sander (11) who studied twins over 60 years of age found that in monozygotic twins the average difference between the two members of a pair in age at death was 36 9 months but in dizygotic twins of the same sex that difference was 78 3

These various studies, using different types of analysis and different populations for study agree in finding that man s length of life is determined in large measure by heredity Dif ferences in that length of life are thus indications of genetic differences among us in ability to resist disease and to cope with the assorted environmental stresses that beset us on our journey through life

Evidence of similar genetic differences in domestic animals is reviewed in the next three chapters.

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Chapter IV

Resistant Little Animals

DOMESTIC animals that have demonstrated genetic resistance to infectious disease or to parasites vary in size from honey bees to horses and represent several different groups in the zoologist's classification I shall consider them in three successive chapters simply as little animals big animals and birds. This unorthodox procedure does not indicate any lack of respect for Linnaeus and his taxonomic successors it is solely a matter of convenience

Resistance of colonies to American foulbrood in honey bees American foulbrood, caused by *Bacillus larvae* is one of the worst diseases with which beekeepers have to contend. At one time it was thought that any colony stricken with this infection could never survive However following numerous reports of colonies that had recovered from the disease, Park *et al.* (3) undertook experiments in which colonies were deliberately infected by removing a rectangular piece of healthy brood and inserting in its place a piece containing not less than 75 scales of American foulbrood. They then selected from the more resistant colonies. In three years of such selection the proportion of colonies apparently able to

withstand the disease was raised from 28 per cent in 1935 to 75 per cent three years later

Subsequent studies by Woodrow and Holst (6) brought out the interesting fact that the apparent resistance of these colonies resulted chiefly from the highly efficient measures taken by their public health officials to prevent the spread of foulbrood. Bees of the resistant colonies were more diligent than others in detecting the disease at early stages, in cleaning out infected cells and in removing diseased brood before the causative bacteria reached the dangerous stage of infectious spores. By these measures which it should be recognized differ little from those used by the medical health officers of other communities to control typhoid fever the responsible officials in the resistant colonies protected their fellow bees from an epizootic catastrophe

While that protection made it possible for the bees of those colonies to pursue their industrious lives with sound minds in sound bodies, it is clear that the apparent resistance was illusory Since the individual bees were protected from exposure to the disease no selection for genetic resistance to it was possible Selection of the kind made by Park and his associates was highly effective in reducing losses from American foulbrood, but it did so not by developing genetically resistant bees, but by breeding public-health officials that were more intelligent and diligent than those in unselected colonies. The possibilities with other species are interesting to contemplate

Resistance of larvae to American foulbrood Evidence that larvae of the honey bee do differ in ability to resist infection has recently been adduced by Rothenbuhler and Thompson (4) Using an ingenious technique in which bee larvae were individually infected with spores of *B larvae* they tested

three different strains of honey bees. One of these the Van Scoy strain had undergone no selection whatever for re sistance to American foulbrood. Another (Chartreuse) had been selected for a single generation only The third strain had been developed by Mr Edward G Brown of Sioux City Iowa, who for many years had exposed the colonies in one of his yards to natural infection with American foulbrood. This he did by allowing them to steal honey from infected combs that had been brought to him for rendering After many generations of this natural exposure, the Brown strain was comparatively resistant to the disease.

Controlled tests of these strains showed that the Brown strain was significantly more resistant than either of the others and that a single generation of selection had made the Chartreuse strain much more resistant than the unselected one (Table 3) Uninoculated control samples of the three

Table 3 Effects of selection in honey bees for resistance to American foulbrood

Strain	Previous selection fo resistance	Larvae inoculated, number	Survived, per cent
Van Scoy	None	178	5
Chartreuse	generation	593	47
Brown	Many years	174	67

From data of Rothenbuhler and Thompson in *Journal of Economic Entomology* 956

strains were equal in viability hence the differences among the infected samples showed that the three strains differed significantly in specific resistance to American foulbrood

As simple mass selection had produced a high level of re sistance in the Brown strain, it seems possible that more carefully controlled matings of survivors from tested stock could result in an even higher level of resistance.

The hardy oysters of Malpeque Bay If the oyster is not a fully accredited domestic animal it is at least one that is cultivated and encouraged. The fact that it is edible delectable, and valuable gives it some standing, but apart from these considerations it has a special value for the purposes of this book The oysters of Prince Edward Island in the Gulf of St. Lawrence have provided a first-class demonstration of the ability of animals to conquer disease when left entirely to their own devices. The most important of these devices, in the case under consideration is probably the ability of single oysters to produce as many as 60 million potential little oysters in a year

The oysters of Malpeque Bay on the north shore of Prince Edward Island are famous across Canada. To that area there came in 1915 a disease which had not been known earlier and for which the causative organism is still unidentified From Malpeque Bay the infection spread around Prince Edward Island probably being helped by oyster fishers who moved overland from one fishing ground to another taking with them their infected gear For the record of gradually increasing resistance to the disease and of critical tests showing that resistance to be genetic in origin we are indebted to the interesting studies of Needler and Logie (2)

When first stricken an area would usually have a mortality rate from the disease of over 90 per cent In some places it was difficult to find a single living oyster on grounds that had previously been crowded. In the early stages of infection there was a cessation of growth a flabbiness of the big adductor muscle and failure to spawn but the most distinctive symptom was the occurrence of yellowish-green pustules, *which appeared in various parts of the oyster and ranged* in size up to half a centimeter in diameter Mortality was highest in late summer and autumn

Wherever this disease appeared, it practically wiped out commercial fishing in the course of a few years. By 1922 it had spread through the Malpeque-Cascumpeque area and in that year no oysters at all were obtained there by commercial fishers. Similar disastrous effects were evident in the Charlottetown area, where the disease first appeared about 1936 Yields in the previous two years had exceeded 8,000 barrels, but by 1939 hardly any oysters of market size could be found and commercial fishing was practically stopped. Eventually the disease spread to all the principal oyster producing areas of the island.

Transfers of oysters from disease free areas to Malpeque Bay in 1928 and 1929 showed that the disease was still present in that area, and the introduced stock proved highly susceptible to it. Out of 60 barrels of oysters introduced from Enmore River in 1929 it was difficult to find later that year as many as 100 oysters for examination.

At the same time the native oysters of Malpeque Bay began to increase in number and by 1930 only about one per thousand showed any of the yellowish-green pustules associated with the disease. In 1925 four barrels of oysters were fished there and in the next year 14 barrels were obtained. From then on, as the recorded yields showed (Fig 12) the number of oysters increased at a remarkable rate, and by 1940 it was far above that obtained in 1915 before the disaster struck

The disease first arrived at Enmore River sometime before 1933 for in that year the fishing was a complete failure. Four years later Needler and Logie brought spat (young oysters) from Malpeque Bay to Enmore River There they were put out on specially devised wire-bottom trays, on which they could be compared in viability with spat of the native Enmore River stock.

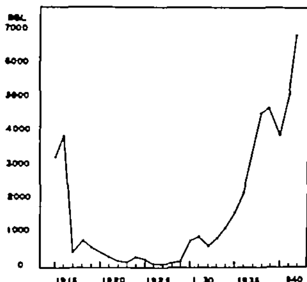


Figure 12. Annual yields of oysters recorded for the eastern part of Prince Cou ty Prince Edward Island, which includes Malpeque Bay They show rapid decline after the disease ppeared in 19 5 and gradual recovery fter 928 as the oysters developed genetic resistance. Because the statistical area includes some south-coast inlets that were not stricken, the figures do not show the full damage in the Malpeque Cascumpeque area, where no oysters whatever were obtained in 922 (After Needler and Logie in *Tr ns- act ns of the Royal Society f Canada* 1947)

As Fig. 13 shows, tests over a period of 10 years proved conclusively that oysters from Malpeque Bay were able to sur vive at Enmore River with normal viability while those of the native stock had extremely low viability from 1936 to 1940 Beginning in 1942 however an improvement was noticed in the viability of the Enmore River stock, and by 1946 results indicated that it was becoming resistant to the disease just as had the oysters of Malpeque Bay In both areas a period of approximately 11 to 13 years was needed to con

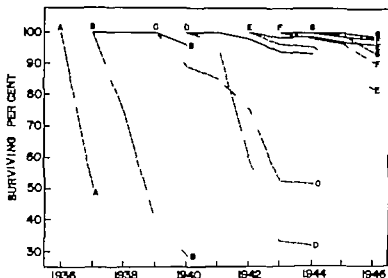


Figure 3 Survival rates for spat from Malpeque Bay (solid lines) and Enmore River (broken lines) in controlled tests at the latter place. They show consistently high viability of the Malpeque stock, original susceptibility of the native oysters, and gradual increase in their resistance to the disease after 94 (After Needler and Logie in *Transactions of the Royal Society of Canada,* 947)

quer the infection and to develop resistant stock. Similar results were obtained at Hillsborough River where spat introduced from Malpeque Bay in 1939 again demonstrated its resistance and where the native Hillsborough River stock was gradually converted from a susceptible strain to a resistant one.

It is probable that over the centuries most species of wild animals have been similarly exposed to pathogenic organisms and have conquered them in much the same manner as did the oysters of Prince Edward Island. Unfortunately with animals less prolific than oysters the process of developing genetic resistance is so slow that most people are unlikely to

observe it in the few decades of observation which any one of us is allowed

This does not mean that the process need be equally slow in large domestic animals. The oysters accomplished their feat by natural selection which is mass selection, i.e the reproduction of resistant individuals without consideration of the records of their families. It is not the most efficient method of improvement since it permits reproduction of surviving individuals in susceptible families and of resistant parents that produce susceptible offspring The handicap imposed upon natural selection by these shortcomings is less serious when nature is dealing with prolific species like the oyster Conversely with domestic animals the slower rate of reproduction is a handicap, but that limitation can be over come by using progeny testing rather than mass selection thus making more rapid progress than is possible by any other means.

Resistant mice In the house mouse so useful for studies of inherited variations in mammals genetic differences among strains have been demonstrated in the ability to resist various infectious diseases. These include piliformis disease (caused by *Bacillus piliformis*) mouse typhoid (caused by *Salmonella typhimurium*) infection by *Salmonella enteritidis* and such virus diseases as louping ill, St. Louis encephalitis, pseudorabies and yellow fever In some cases strains originally susceptible have been made highly resistant by a few generations of progeny testing Thus, Schott raised the resistance of mice to typhoid from 18 to 75 per cent in six generations and later investigators brought resistance up to 92 per cent. In most cases resistance to infectious disease in mice appears to be dependent upon many genes. In others as with the 17 D strain of yellow-fever virus studied by Sabin (5) resistant

mice apparently differ from susceptible ones by only a single gene.

Much of the literature on resistance to disease in rodents has been reviewed by Gowen (*1*) In order to save the space for animals that are bigger or more palatable it will not be covered here

Disease resistance in larger rodents Genetic resistance to infectious disease has also been demonstrated in rats guinea pigs, and rabbits The last two of these species are susceptible to the bacillus causing tuberculosis in man but in both some strains have been shown to be more resistant than others Inbred strains of rats were found to differ greatly in susceptibility to the large tapeworm, *Taenia taeniaformis* and hence to the tumors caused by the cysticerci of that parasite

Interesting experiments are provided by attempts in Australia and elsewhere to eliminate unwanted rabbits by turning loose among them the virus causing myxomatosis. When that disease was first released in Australia it is reported to have killed some 99 per cent of its targets. A few years later in 1953 investigators found that in areas around Canberra its lethality had dropped to about 50 per cent. There are indications that in some districts the virulence of the virus may have lessened. Whether that is a factor or not it seems probable that the initial heavy mortality permitted survival of only the most highly resistant rabbits and that descendants of these with the prolific reproduction of their species will eventually beget a race of rabbits perhaps not bigger or fiercer but certainly biologically more fit to survive than any that Australia had known before

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Chapter V

Resistant Big Animals

ANY laboratory geneticist accustomed to carrying out well-controlled experiments with his hundreds of mice or rats may well view with a somewhat critical eye the experiments reported in this chapter One must remember however that large domestic mammals are expensive and comparatively slow to reproduce and that they require much more space and labor for their management than do the convenient laboratory mammals However it is difficult to persuade a farmer to breed for resistance to disease by relating the wonders that have been accomplished with fruit flies and mice. Cows and even chickens command somewhat more respectful attention

Considering these difficulties and also the fact that the orthodox controllers of disease generally prefer to dispose of reactors and *certainly not to infect* healthy animals intentionally it is a sign of progress that two experiments can be reported here in which investigators deliberately infected large domestic animals in a search for genetic resistance and then multiplied the resistant stock.

The sequence of events lead ng to the development of a resistant strain usually includes the following steps

1. Recognition during an outbreak of some disease that certain animals come through unscathed.
2. The discovery that such resistant animals are often related.
3. Multiplication of the resistant stock and continued selection to develop a resistant strain.

Evidence of genetic differences in resistance to disease is also afforded whenever different breeds are simultaneously exposed to some disease and one of them proves to be more resistant than others.

For convenience the evidence from all sources will be considered here by species of domestic animals rather than by any grouping of diseases of similar origin

SWINE

Brucellosis or abortion *Brucella suis* sometimes causes considerable financial loss from abortion even though infected animals often recover and reproduce without trouble. Chronic infection causes arthritis and frequently in boars orchitis.

In 1929 an outbreak of brucellosis in the Berkshire herd of the University of California left half the herd reactors to tests for *B suis* Non reactors were kept for breeding, and their descendants remained free of infection Tests in 1942 showed that after artificial inoculation the 18 animals tested were all negative (Cameron *et al* 5) In their interesting studies of genetic resistance to brucellosis in swine Cameron *et al* used a relatively simple method of distinguishing between resistant and susceptible pigs The animals under test were inoculated orally at about 10 weeks of age and 2 weeks later agglutination tests were made to find which animals reacted to the test. A negative test indicating the absence of agglutinins against *B suis* was considered to indicate re

sistance. A consistent reaction in the highest dilution was considered positive.

Two negative grade sows that had originated from the purebred Berkshires of the University of California herd were bred to a male that had shown only a very weak reaction. Their 33 offspring, which comprised the first selected generation, were compared with unselected controls. The results were as follows

	Pigs tested	Reactors
First selected generation	33	27 per cent
Unselected controls	31	91 per cent

The comparatively high resistance of the selected stock is remarkable considering that these animals were the products of simple mass selection in one generation only.

In subsequent matings of resistant females with three different boars that had proved resistant (Table 4) only one

T ble 4 Resistance to B suis in progeny from matings of resistant parents

Matings of resistant ♀♀	Progeny				
	Litters	Pigs tested	Resistant	Uncertain	Susceptible
With ♂ 4 (weak reactor)	8	4	5[illegible]		
2 With resistant ♂ 9		6[illegible]	49	3	0
3 With resistant ♂ 33 (Duroc Jersey)	5	24	7	6	
Total and percentages	[illegible]3	[illegible]8	76.6%	[illegible] 6%	8%

From data of Cameron et al. in Journal of Animal Science 91

definite reactor was encountered among 128 offspring It is worth noting particularly that Sire 4 which showed a reaction in the lower dilutions only produced offspring that were just as resistant as those from the non reactors. Resistant animals were found among Duroc Jerseys Poland Chinas, and Berkshires.

Because of these and similar results, Cameron and his associates (2) concluded that "brucellosis in swine can be controlled under average field conditions by the use of lines that are genetically resistant to *Brucella suis* To do this effectively Cameron (1) recommended the following procedure In infected herds young pigs should be weaned at 8 weeks of age and tested individually by the agglutination test. Those negative to that test should be removed from the infected herd to some location isolated from the parent stock. As additional litters come along, non reactors can be added to the isolated herd. Pigs in that herd should be tested periodically and any reactors removed at once When the non-reactors reach breeding age they can be bred to boars known to be negative to the test for *B suis* Meanwhile the original herd is disposed of as soon as the isolated herd has grown to sufficient size This method of control has worked well in California, and Hutchings and Washko (16) have confirmed its efficacy elsewhere

While this procedure utilizes the non reacting (and presumably more resistant) pigs and excludes the reactors from reproduction it is essentially a method for starting a new isolated herd with uninfected stock. Since in genetic terms it represents only a single generation of mass selection one could hardly expect that the non reacting parents would beget only resistant stock. This was recognized by Cameron, who recommended repeated blood testing of the isolated herd.

In general, resistance to infection seems to depend upon polygenic inheritance rather than on a single pair of genes and in such cases several generations of selection would usually be necessary to develop a high degree of resistance It would be of interest to determine how much the incidence of reactors in an exposed herd could be reduced by four or five generations of progeny testing, but this has apparently not yet been tried

Resistance to brucellosis is genetically determined in rabbits also. Manresa (20) found resistance to be dominant to susceptibility with some indication that the difference between the two classes is determined by a single pair of genes

Erysipelas In areas where losses from this disease are serious the usual preventive treatment according to Hagan and Bruner (15) is to inoculate with the causative organism (*Erysipelothrix rhusiopathiae*) and at the same time to give immune serum from pigs that have survived infection. While the method is effective, some pathologists dislike the practice of treating animals with living pathogenic organisms even though protection is administered simultaneously

One of the difficulties impeding earlier studies of swine erysipelas was that inoculation did not regularly cause the disease nor did feeding the causative organism. This was overcome by Professor Joseph Fortner of the Robert Koch Institute in Berlin who devised a method of uniformly inducing erysipelas by scarifying the skin before inoculation He then went on to demonstrate that some pigs are genetically resistant to such inoculation while others succumb (10) To ensure adequate tests in this work, each experimental animal was inoculated with material from 5 to 8 different strains of the causative organism

Fortner's experiments illustrate the difficulty of carrying

out with large domestic mammals experiments that would be simple with mice and some detailed account of them is justified He and Wellmann (12) found remarkable variation among different litters in response to inoculation (Table 5)

Table 5 Varying resistance to erysipelas in samples from different litters

Breed	Inoculated, number	Local reaction number	Generalized skin lesions, number	Chronic effects, number	Died, number
Various					
4 resistant litters	18	18	5	0	0
5 other litters	15	15	5		1
Infected sow No. 251	9	0	0	0	0
German Landrace					
5 resistant litters	18	18	16	5	0
4 other litters	24	24	22	4	10

From data f Fortner and Wellman In *Monatshefte für praktische T erheilkunde* 1952.

All the pigs showed a localized skin reaction at the site of inoculation and developed fever—except the nine litter mates from sow No 251 A previous litter from the same sow had also been completely unaffected by inoculation. Since she herself had severe chronic arthritis as an aftermath of her own inoculation it was concluded that she had retained the infection and had transmitted passive immunity to her two litters. Whether such a transfer of protective antibodies occurs before birth or after birth through the milk was not determined.

The two litters from this sow provided important evidence In studies of genetic resistance to disease in mammals and birds, it is necessary to know whether the resistant animals have an active resistance as a result of their genetic con-

stitution or merely a passive resistance because of protective antibodies from their dams. With respect to erysipelas it seems probable from these two litters that passive immunity protects inoculated pigs from even local reactions at the site of inoculation. Conversely when such local reactions do occur as they did in all 72 pigs of the 14 other litters considered in Table 5 (and in others tested earlier) they are



Figure 14 Generalized lesions of the skin caused by swine erysipelas. (From Hagan and Bruner *The Infectious Diseases of Domestic Animals* 1957 courtesy of R. A. McIntosh.)

likely to be indications that the pig does not carry passive immunity and hence that its subsequent response whether recovery or otherwise, is a measure of its genetic constitution.

Among these 14 other litters response to inoculation varied greatly among and within litters The most resistant animals showed only skin reactions, localized at the site of inoculation along with temporary fever Others developed generalized skin lesions (Fig 14) but recovered completely Some developed septicemia and died. A few of those that recovered

showed chronic arthritis. In samples of 2 2 5, and 9 pigs from four litters all the animals recovered at the other extreme all 6 pigs inoculated in one litter died within 3 days.

By breeding from resistant animals and from those that produced mainly resistant offspring, Fortner (10) developed a highly resistant strain The record as summarized by the present author from Fortner s reports (Table 6) is far from

Table 6 Erysipelas in unselected stock and in pigs bred for resistance

Period	Stock	Inoculated, *number*	Generalized skin lesions, not fatal, number	Septicemia, died or destroyed number
943–45	Unselected	98	25	24
1946–48	Resistant line	85	0	0
1946	Control	52	Many severely stricken some died"	
Cumulative to Feb 1 953	Resistant line No. 26 litters	58	some	0

From data of Fortner in *Berliner u Münchener tierärztliche Wochenschrift* 949, and personal communication.

complete, and the controls are scarcely adequate but it is one thing to conduct a controlled laboratory experiment with mice and quite a different matter to make comparable tests with animals as large as pigs. This is particularly true when the controls must be infected with a pathogenic organism A test in 1946 of 52 pigs apparently intended as controls caused such severe illness that when it became known a current of uneasiness spread among the farmers !

In spite of these shortcomings in the experiments, the fact is highly significant that in Fortner s No 1 strain every one of the 158 animals tested from 26 litters recovered completely without any trace whatever of the endocarditis or

arthritis frequently found in older animals afflicted with the chronic form of erysipelas (11)

To this brief summary Fortner's view of the practical applications of his experiments should be added

> The practical pplication, which now in my opinion is evident from these experimental studies of erysipelas in our specially bred line of pigs, is that breeders should take care to find the pigs endowed with natural resistance, to give them preference as breeders, and thus to develop a stock which no longer needs the protection of inoculation [10, p. 58].

Had this recommendation come from a geneticist it might be considered by orthodox veterinarians as just one more example of the ridiculous extremes to which heretical geneticists can go Since it came from a veterinarian and from one with many years of experience with the disease of which he wrote one is perhaps justified in hoping that it may induce his professional colleagues to think of the possibility of controlling disease by the utilization of genetic resistance whenever it is practicable to do so.

Hog cholera. Some evidence has been reported by Manresa and Mondonedo (21) that the Berkjala breed developed in the Philippine Islands from crosses of Berkshires with native pigs, may be more resistant to hog cholera there than are breeds introduced from other countries. During an outbreak of that disease in herds at a prison farm, mortality over a 5 month period was 80 per cent in Duroc Jerseys, 59 in Poland Chinas, but only 48 in Berkjalas. However since these three breeds had earlier shown corresponding differences (but with much lower mortality) in deaths from other causes, it is not clear that the Berkjalas are specifically resistant to cholera. The record does prove beyond question

that the Berkjalas are more viable under Philippine conditions than the other two breeds are.

The attempts of Lambert *et al* (17) to raise resistance to cholera by breeding from pigs that survived experimental inoculation were not conspicuously successful It seems evident that in their work difficulty in standardizing the dosage was a limiting factor and it is scarcely surprising that simple mass selection failed to show results in one generation

Dysentery Engelhart (9) has reported a peculiar susceptibility of young pigs to a type of dysentery (*Ferkelruhr*) attributed exclusively to heredity Over a period of four years 5 boars were each mated with some or all of 18 sows, and records were available for 81 litters. Three of the boars sired 408 piglets that were alive 1 week after birth and among these although 8 died, none had dysentery The other two boars produced only susceptible offspring to the number of 338 of which 66 died. Some sows produced by one boar only healthy piglets, by the next only susceptible ones and, later by another boar only healthy offspring again The dysentery was unrelated to season age of sow or environment Such all-or none susceptibility of whole litters is difficult to explain by any genetic mechanism and further studies seem desirable.

SHEEP AND GOATS

Infectious pulmonary adenomatosis or jaagsiekte An interesting record of what happens when a new disease is introduced to a previously unexposed population has come to us from Iceland A number of Karakul sheep were imported into that island in 1933 from the Dairy Institute at Halle in Germany They were kept in quarantine for some time but

later were distributed to 16 different farms scattered through the country The record of what followed has been given by Dungal *et al* (7) and by Pálsson (25) In 1934 one of the im ported rams was found to be suffering from a respiratory disease, and later that year and in the next the sheep on that farm developed the same symptoms and many died. During the next three years the disease spread through many parts of the country killing from 25 to 80 per cent of the afflicted flocks. Average mortality was around 50 per cent. In attempt ing to diagnose the new disease, Dungal *et al.* compared it with other pulmonary disorders and found it to resemble the disease known in South Africa (and elsewhere) as *jaagsiekte* in every respect except one the mortality rate in the Icelandic sheep was many times that found in other parts of the world. Subsequent studies confirmed the indica tions that the two conditions are identical.

Characteristic symptoms of this disease include dyspnea, which becomes progressively worse and is accompanied by the excretion of watery mucus from the respiratory passages. There is no fever but when the disease has reached an ad vanced stage the breathing causes a characteristic sound which may be heard by anyone standing in the midst of the affected flock, the multiple râles resembling the sound of slowly boiling porridge.

The possibility of eradicating the disease by slaughter was considered but soon dismissed partly because of the cost but also because it was too dangerous to move unexposed sheep into infected areas to replace those that had been slaughtered. It was observed, however that some families or strains were more resistant to the disease than others and investigations during 1938 to 1945 confirmed this fact. The Gottorp strain, which was popular and widespread, was recognized as being

particularly susceptible In contrast, the Adalból strain was found to be unusually resistant. One farmer lost 80 of 100 sheep of his own strain (not Adalbols) but among 25 of the Adalból strain in the same flock only one died. Similar resistance in that strain was demonstrated elsewhere. On one farm where careful pedigrees were kept significant differences were evident among rams in the ability of their progeny to withstand the infection. The figures as given by Dungal *et al* (7) are as follows

Name of ram	*Progeny number*	*Mortality per cent*
Erpur (Gottorp strain)	82	93 9
Ljomi	37	40 9
Odinn	53	5 5
Kimbi	48	66.7
Kolur	41	51 5
Adils (Adalból strain)	20	10.0
Various others	171	60.3
Total	458	61.1

Unfortunately the Adalból strain so desirable because of its high degree of resistance, was not widely distributed at the time when adenomatosis struck.

To combat the new disease farmers were advised to breed from resistant families and to kill all rams from susceptible families. It was noticed that the mortality rate remained about the same during the first two years after appearance of the disease in a flock where it had not previously been known. Thereafter the rate of mortality decreased gradually presumably because of natural selection i.e early elimination of the susceptible sheep and consequent restriction of reproduction to the more resistant ones.

This is illustrated by Pálsson s record (Table 7) for flocks

stricken in 1936 In these figures it would appear that, since the period in which mortality was measured must have been shortened somewhat for each successive annual crop of ewes,

Table 7 Decline in mortality from adenomatosis i flocks first stricken in 936

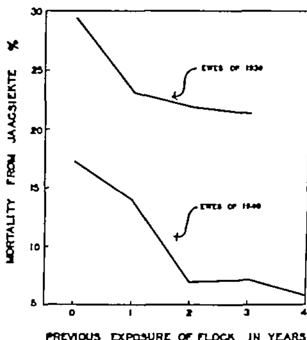
Ewes of year	Number	Mortality to Jan, 941	
		From adenomatosis, per cent	From other causes, per cent
936	,488	66.5	7
937	783	5 7	4 6
938	4,24	39 0	4 6
939	6,355	2 .5	3 9
194	6,280	6 0	3

From data of Pálsson in Haskoli, Islands, Atvinnudeild, *R t Landbunadardeildar* 943.

not all of the decline in mortality can be attributed to increasing genetic resistance During the five years from 1936 to 1940 however the mortality from other causes declined relatively less than that from adenomatosis, which decreased from 66 to 6 per cent. Mortality from residual causes was lower by 50 per cent for the ewes of 1940 than it was for the ewes of 1938 probably because of the shorter period of test, but the corresponding reduction of mortality from adenomatosis was 85 per cent. Clearly the resistance of the stock was increasing.

The same trend is shown by Pálsson s record of mortality for ewes of 1939 and of 1940 as given separately for flocks with differing degrees of previous exposure to adenomatosis (Fig 15) Mortality was consistently lowest for flocks in which the disease had been present for two years or more.

Adenomatosis is apparently not a serious source of loss in other parts of the world where it has long been present. Its disastrous effect on the Icelandic sheep can best be explained



F gure 5 Mortality from *jaagsiekte* (adenomatosis) to January 1 1942 wa highest i flocks not previously exposed and lowest in those exposed longest. Ewes of 939 were tested ne year longer than those of 1940, hence they show higher mortality (Drawn from data of Pálsson s report, cited in references.)

by the fact that they had not previously been exposed and hence had experienced no natural selection Somewhat simi larly measles and chicken pox are not serious diseases in most parts of the world, but they wrought havoc among the Indians of North America when introduced there by white invaders

from Europe Adenomatosis has been found in the United States, but it is highly probable that any chance that the genetically resistant sheep in affected flocks in this country will be allowed to demonstrate their biological superiority is something less than that of the proverbial snowball in Hades.

It should be recognized that the situation confronting the sheep of Iceland when first stricken with adenomatosis was approximately the same as that of the oysters of Malpeque Bay considered in the previous chapter The oysters developed what appeared to be complete genetic resistance to the disease in about a dozen years the Icelandic sheep because of their slower rate of reproduction will probably need more time. If, however selection is made on a family basis, it is entirely possible that their resistance can eventually be raised to a point at which losses are not serious Evidently that same degree of resistance has already been reached in stock long exposed in other parts of the world.

Resistance to trichostrongyle worms The Romney Marsh sheep bred in the area of Kent after which they are named are unusually resistant to stomach worms of the family Trichostrongylidae. This is known to the farmers of the area, some of whom would apparently prefer to keep other breeds but cannot afford to do so because no breed is as well able as the Romney Marsh to survive the high degree of parasitism inevitable in the lush pastures of the Romney Marsh area. Some years ago Dr E. L. Taylor of the Veterinary Laboratory at Weybridge England, told me that he had seen Romneys grazing in the same fields with sheep of other breeds, when the latter were in extremely bad condition because of parasitism while the Romneys appeared to be in perfect health.

Experimental evidence of that resistance which is now a breed characteristic of the Romneys was obtained in faraway

California by Stewart *et al* (51). From each of five different breeds, five or six lambs were kept together under identical conditions in one flock. Over a period of 12 months the degree of infestation by the worm *Ostertagia circumcincta* in each lamb was measured by counting at regular fortnightly intervals, the number of worm eggs per gram of feces. The studies showed, not only that the worm-egg counts in the Romneys were significantly lower than those in any of the other breeds but that among the Shropshires, Southdowns, and Hampshires for which the breed averages were comparatively high there were one or two individuals for which the counts were not significantly higher than the mean for the Romneys (Fig 16) In other words there were some highly resistant individuals even in the most susceptible breeds. An

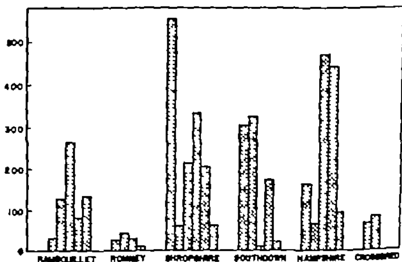


Figure 16 Average counts of worm eggs showing varying degrees of infestation in representatives of four breeds but uniformly low counts in the Romneys. Each column represents one animal. (After Gregory in *Proceedings of the American Society of Animal Production* 1937)

important point to determine as Gregory (13) has pointed out, is whether or not resistance to *O circumcincta* carries with it resistance to other worms particularly to *Haemonchus contortus* which is a serious parasite in some sections of the United States and elsewhere

The Romney Marsh sheep provide one more case in which domestic animals under natural selection have developed a high degree of resistance to some infection It is entirely possible of course that over the years the farmers in the Romney Marsh area have not left the entire responsibility to nature but have helped the good cause along by some selec tion for resistance on their own.

Further evidence of genetic differences in resistance to nematode worms was found by Gregory *et al.* (14) and by Whitlock (36) who determined the severity of infestation with trichostrongyle worms of any kind in lambs of different sire families In Gregory's Hampshires the progeny of one ram had consistently fewer worm eggs per gram of feces over an 8-week period than did daughters of another ram Among six rams whose 125 progeny ran together in a common pas- ture Whitlock found that one of them, Violet (*sic*!) had sired comparatively resistant lambs, another begot highly suscepti ble progeny and four were intermediate.

Over a nine-year period in which Warwick *et al.* (34) com pared the progeny of rams and ewes resistant to the worm *H contortus* with unselected controls, the selected stock proved significantly better able to withstand infestation than the con trols. However resistant rams mated with unselected ewes did not produce resistant lambs, a fact showing that resistance is polygenic, and hence that, to be effective selection must be exerted in parent stock of both sexes Selection for resistance to the same worm was apparently somewhat more effective in

goats than in sheep. The percentages of goats surviving infestation in progeny from two different kinds of matings were as follows

	Selected	Unselected controls
Resistant ♂♂ × unselected ♀♀	71	55
Resistant ♂♂ × untested daughters of resistant ♀♀	85	51

An important fact brought out in these studies was that unimproved sheep used in crosses effectively raised the level of resistance, but only at the expense of a lower yield of wool. Following selection for both desirable qualities some of the resistant sheep and goats were approaching standard yields of wool and mohair

As phenothiazine for many years the standard anthelmintic treatment for stomach worms in sheep and goats does not kill all the worms but only reduces them to a number that the animal can tolerate It is quite probable that it acts as an instrument of selection whereby only the more susceptible worms are killed, leaving the resistant ones to flourish—and to reproduce If resistant races of worms should eventually prove better able to withstand increasing doses of phenothiazine than their hosts one solution might be to find a new drug Another could be to breed resistant sheep Both measures combined might be more effective than either one alone

CATTLE

Mastitis A committee of the American Dairy Science Association meeting at Storrs, Connecticut in 1956 concluded that mastitis is the most costly disease of dairy cattle not under satisfactory control Mastitis is a general term for infection of the udder According to Murphy (23) there are four distinctly different kinds of infection which comprise some 99

per cent of all the cases clinically diagnosed as mastitis. These infections are caused by *Streptococcus agalactiae* and by other streptococci staphylococci, and bacilli.

For years the standard treatments for mastitis have included disinfection, sanitation and every effort to avoid injuries to the udder Until comparatively recent years it was a common practice to test milk for *S agalactiae* and to eliminate cows shedding that organism. With the advent of antibiotics a new era dawned In the advertising pages of every farm paper dairymen were adjured to solve all their problems with the very latest mixture of high-powered antibiotics. Since this had been going on for several years prior to the meeting referred to above it is surprising, perhaps, to find that in 1956 a committee of the American Dairy Science Association should still regard mastitis as not being under satisfactory control.

Although little or no use of the fact has yet been made in practice, it has been established that susceptibility to udder infection is genetically determined. As usual the first indications of this fact were provided by certain highly susceptible families that were recognized as such by careful observers. In the dairy herd of the agricultural college at Hohenheim, Germany Zieger (88) found that over a period of years one cow and *her nine female descendants* all developed streptococcal mastitis, while another cow and her eight descendants remained completely free Both cow families were kept concurrently and their members had equal opportunities for infection White and Ibsen (85) reported that, among several hundred cows bred at the Alaska Agricultural Experiment Station from crosses of Holstein and Galloway cattle, only three cases of acute mastitis were encountered, and these occurred in a cow *her daughter and her granddaughter*

Similarly in studying a herd of 60 Guernsey cows during a

period of six years, Murphy *et al* (24) observed a remarkable difference between two cow families in susceptibility to infection of the udder (Table 8) The degree of resistance or

Table 8 Familial difference in resistance to infection of the udder by streptococci and staphylococci

Cow			Her daughters		
Designation	Lactation periods observed, number	Proportion of milking time infected per cent	Designation	Lactation periods observed, number	Proportion of milking time infected, per cent
Number 283	5	100	A	4	50.0
			B	5	80 4
			C		83 3
Number 247	7	0	D	5	2.5
			E	4	.8
			F	4	12.5
			G	2	6.7

From data of Murphy *et al.* in *Cornell Veterinarian* 1944

susceptibility was measured by the proportion of the lactation periods during which the udder showed infection with streptococci or staphylococci as determined by regular bacteriological examinations It is clear that the highly resistant cow No 247 produced comparatively resistant daughters, while the other cow herself highly susceptible produced only susceptible ones.

Using the leucocyte count in the milk as a measure of the degree of udder infection Ward (32) made an extensive study of the incidence of mastitis in dams and their daughters. The best cows were those known to be free of infection for at least eight years, and the others were classified as A, B, or C, with A indicating the lowest degree of infection or none at all and C the highest. Among daughters of these

cows the proportions found to be susceptible (in Classes B or C) were as follows

	Daughters number	Susceptible per cent
From dams free 8 years	89	27
From dams of Class A	250	24
From dams of Class B	168	50
From dams of Class C	281	61

As these data show the highly susceptible dams of Classes B and C produced almost twice as many daughters in that same category as did the comparatively resistant dams in the other two classes.

Further studies in which all dams and daughters in the herds under investigation were classified either as resistant or susceptible were later made by Ward (35) in two different districts of New Zealand. A somewhat similar investigation was made by Legates and Grinnells (19) in North Carolina. In his work Ward classified as susceptible any cows that developed clinical mastitis at an early age or retained infection in one quarter for 5 months or more or were affected in any quarter on more than one occasion Legates and Grinnells classified as susceptible those cows which during the period of sampling, showed a leucocyte count of 500,000 or more per milliliter in the milk from any quarter and also demonstrable streptococci or staphylococci. In spite of these differences in classification, Ward's findings in New Zealand were confirmed by the studies in North Carolina (Table 9) The data from all three areas are consistent in showing a significant tendency for susceptible dams to produce susceptible daughters and for resistant cows to beget progeny endowed with better than average resistance.

In the herds considered in Table 9, the data in effect show the results of a single generation of mass selection among

Table 9. Data showing tendency of cows resistant to mastitis to produce resistant daughters

Investigator and place	Herds, number	Susceptible dams		Resistant dams	
		Number	Susceptible daughters, per cent	Number	Susceptible daughters, per cent
Ward, Canterbury N.Z.	10	88	89.5	109	58
Ward, Manawatu N.Z.	5	28	81.3	17	51.4
Legates and Grinnells, North Carolina, U.S.A.		141	55.0	81	35.0

dams only without consideration of the inheritance from the sire. And yet as Reid (27) has shown, there are significant differences among sires in the degree of genetic resistance to mastitis that they transmit to their daughters. Because their sires were unselected (so far as resistance to mastitis is concerned) the significant decrease in the susceptibility of daughters from the resistant dams is all the more remarkable If, in addition to selection on the dam's side of the pedigree, similar selection could be made among sires so that only sires that transmit a high degree of resistance would be used the proportion of susceptible offspring should be reduced to still lower figures even in the first selected generation From the results of similar selection experiments with other species, it is reasonable to expect that the cumulative effects of several generations of such selection would reduce the incidence of mastitis to a level not economically serious. Unfortunately to the best of my knowledge apart from experimental studies no such deliberate identification of sires as transmitters of resistance or susceptibility has yet been carried out. Here lies

a great opportunity for some of the many centers through which artifical insemination of dairy cows is carried out on an extensive scale.

To this brief survey of the evidence that resistance and susceptibility to mastitis depend in large measure upon the genes that the cow carries it is a pleasure to add the contribution made by Professor J J Reid (2,) of Pennsylvania State University Neither a geneticist nor a veterinarian, Reid's approach to the problem was that of a bacteriologist attempting to find the underlying causes for bovine mastitis and also measures for controlling it. To that end over a 10-year period he utilized over 2,000 animals in 46 herds some of which were under study for more than 8 years In some of these herds attempts were made to follow all of the standard recommendations but in others some of these practices were ignored. His conclusion about them was that

whatever useful purpose such measures may serve they do not in practical application effectively control mastitis. In fact, low incidence seemed to be characteristic of certain farms where the animals were bedded on manure which had been collecting for months and little attention paid to sanitation in general. On the other hand relatively high incidence seemed at times to be associated with extreme stress on sanitation. It should not be inferred from this that the dairymen should ignore sanitation common sense dictates the use of sanitary practices in the production of milk of good quality It should be noted, however that such practices have little if indeed any relationship to the control of udder trouble.

For sheer undiluted heresy in the field of disease control it would be difficult to match the following headings of sections in Reid's bulletin

Sanitation fails to reduce incidence
Disinfection of udders, teats and teat cups ineffective
Bactericides useless in udder washes
Cleaning and disinfecting stable floors of no avail
Segregation of mastitic cows helps very little

It is possible that these forthright statements may not be wholeheartedly endorsed by the people who have been hopefully attempting for years to reduce mastitis by the very measures that Reid found to be futile. Nevertheless, one wonders to what extent abiding faith in those same measures is responsible for the fact that mastitis was recently designated the most costly disease of dairy cattle *not under satisfactory control*" (italics mine)

From his 10-year study of mastitis in the herds of Pennsylvania State University Reid concluded that a major factor influencing the occurrence of mastitis is heredity Among 18 Jersey heifers from one sire the incidence of mastitis was 55 per cent whereas among the 15 heifers from other sires its frequency was less than 14 per cent. Although the numbers are small the statistical odds against such a difference occurring by chance alone are more than 20 to 1 The fact that the first bull was transmitting susceptibility was not recognized until he had left the University herd Used elsewhere he left a trail of mastitis that was called to the attention of the author on several occasions. Perhaps nothing better could be expected from a bull whose name was Imported Dreaming Cowslip!

In the Holstein-Friesians of the University herd similar familial differences in the incidence of udder infection were evident. In 79 of them representing 11 female lines" with four cows or more in each the proportions showing mastitis and infection with *S agalactiae* were as follows

	Mastitis per cent	S agalactiae, per cent
In all 79 cows	4 8	5.2
In Line 1 (23 cows)	21 7	8.7
In Line 10 (7 cows)	85.7	7 4

The difference between Lines 1 and 10 in ability to resist infection was also evident in the average ages at which infection with *S agalactiae* developed. These were 7 6 years for the resistant Line 1 but only 3.8 for the susceptible Line 10

Among 36 Ayrshires in the University herd, only one animal became infected with *S agalactiae* during the course of Reid's study It would be interesting to get further evidence on the question whether or not Ayrshires as a breed are any more resistant to such infection than others.

It is to be expected that, even though susceptibility to mastitis is genetically determined, the incidence of infection can be increased, as with other infections by various adverse environmental conditions. In Reid's experience these include poor milking practices, poor housing, lack of adequate bedding, exposure to inclement weather and mechanical injury all indicating disregard for the comfort of the cow Another important variable, and one that may make the differentiation of resistant and susceptible cows difficult is that susceptibility to mastitis increases with age.

Tuberculosis As stated earlier resistance and susceptibility to tuberculosis in man in guinea pigs, and in rabbits are determined in large measure by heredity It would not be surprising, therefore, if the same should apply to cattle and there is ample evidence that it does. As usual, certain families in infected herds have been found to be significantly more resistant to disease than others.

In a herd of Simmentals, Ruppert (28) found the incidence

of tuberculosis among 34 daughters of one sire to be 61 8 per cent while at the same time the incidence in 25 daughters of another sire was only 4 per cent. Since the animals of the herd were intermingled the difference could not be attributed to any variation in the environment or in exposure and was clearly dependent on differing genotypes with respect to susceptibility Similarly Ehrlich (8) in making a careful study of a large herd of Black Pied Lowland cattle found that over a five-year period the average number of cases per year was 21 per cent of the cows in the herd. Among the offspring of 25 animals that produced susceptible progeny the corresponding incidence was 57 6 per cent. Here again all animals were kept under similar conditions, and the difference in susceptibility could be attributed only to hereditary predisposition.

Zebu cattle in addition to their many other virtues, are remarkably resistant to tuberculosis. The literature on that subject which indicates that tuberculosis in cattle of the Zebu type in India is comparatively uncommon has been reviewed by Carmichael (4 5) He reported further on the incidence of that disease in Ankole and Zebu cattle in Uganda Up to 1918 only a single case of tuberculosis had been identified in Uganda but beginning about 1929 it spread through large areas of the country Carmichael reports that among cattle of the two types examined post mortem from 1931 to 1936 the incidence of tuberculosis was as follows

	Animals number	*Tuberculosis per cent*
In Ankole cattle	6 185	1,0
In Zebus	26,979	0.9

Similarly the proportion (percentage) of animals showing a positive reaction to the intradermal test was 55 in Ankoles

but only 0 6 in Zebus and 6.9 in intermediates Among eight Zebu calves inoculated experimentally only one died, but three Ankole calves similarly treated all died, one of them as early as 3 weeks after inoculation

While the evidence is conclusive that resistance to tuberculosis in cattle depends upon genes as it does in other species, the extent to which that information can be utilized varies somewhat in different parts of the world. In many parts of North America and some parts of the British Isles tuberculosis has been eradicated. No geneticist would suggest that in clean areas such as these any attempt should be made to breed resistant stock. On the other hand there are many parts of the world in which tuberculosis is enzootic, and there it would seem that one effective way to reduce the incidence of the disease would be to multiply the genetically resistant stock. Undoubtedly natural selection is following that program, but it could be expedited by special care to give preference for reproduction to the animals that have demonstrated resistance.

Protozoan diseases The Zebus are known to be much more resistant than are European breeds to tick borne protozoan infections, particularly piroplasmosis and anaplasmosis Zuravok (39) reported that among 46 hybrids from a cross of Zebus × Red German cattle tested in Azerbaijan, a tick infested region most of the animals showed only mild symptoms of the tick borne diseases, and all but three recovered The animals were tested by natural exposure and were also infected artificially by tick bite or inoculation. Those infected with *Babesia* and *Anaplasma* organisms all recovered, and the three fatal cases died of theileriasis. If the characteristic resistance of the Zebus to tick borne diseases is thus transmitted in large measure to all of their first-generation

hybrids, the products of such crosses should be remarkably useful in the extensive tick infested areas of the world. One possible basis for this resistance together with Bonsma's evidence that cattle of the Zebu type are more resistant than other cattle to heartwater is discussed in Chapter VIII

West African Shorthorns, a comparatively small breed partly of Zebu blood are much more resistant to trypanosomiasis than are cattle from areas where the tsetse fly which carries the trypanosomes is not prevalent. According to Stewart (50) whose long experience as Director of Veterinary Services in the Gold Coast gives special value to his statements the resistance of the West African Shorthorns is to trypanosomes in general and not merely to those of the local area in which the cattle were bred. He considered that such resistant cattle should have a special value for other parts of Africa where the tsetse fly abounds. The N'Dama cattle of French Guinea are also known for their resistance to trypanosomiasis.

In the West African Shorthorns, according to Stewart their Zebu blood, so far as resistance to trypanosomiasis is concerned, is a liability rather than an asset Those with the least Zebu blood are the most resistant. Among 1 151 cattle observed at the Pong Tomale Station during four outbreaks of trypanosomiasis, only 171 became infected 62 showed clinical signs, and only 11 died Of the 62 that showed clinical signs a disproportionately high number (45) were Sangas, which had a higher content of Zebu blood than the other cattle at the station

Foot-and mouth disease During an outbreak of foot-and mouth disease in France in 1938 all animals in a herd of Charollais except one cow contracted the disease That one cow remained in good condition although constantly ex

posed. Fourteen years later during another bad outbreak the same herd was again stricken but Prat (26) observed that this time there were three animals that were completely resistant and three others that showed only mild symptoms for a few days at most. Milk production was not affected. All of these six resistant animals were descendants of the original resistant cow of the 1938 epizootic Three of them were granddaughters of the original one, but two others were great-granddaughters. It is remarkable that the genetic resistance displayed in 1938 should be carried down to a third generation Prat also reported that in a neighboring county the veterinarian had found that daughters of one bull were notably resistant to foot-and-mouth disease

By itself this evidence is little more than a straw showing how the wind blows. It may be of little importance in a country like the United States where official veterinarians stand guard at every port and boundary to make sure that foot-and mouth disease shall not enter the country and that if it does elude them it is immediately stamped out The same applies to Australia where there has apparently been no foot-and mouth disease since 1872 On the other hand, in a large part of the land surface of the globe foot-and-mouth disease is enzootic. Even in places where every attempt is made to stamp it out by slaughter the disease seems to pursue its epizootic way about every dozen years. In such areas it would seem very much worth while to determine how quickly control could be accomplished by the development of genetically resistant stock. Presumably this could not be done in areas where control by eradication is being attempted. However if in the United States an isolated island can be set aside for study of the disease surely somewhere in the world it should be possible to set aside another isolated laboratory like the present one on Plum Island, on which veterinarians and

geneticists working together might investigate the feasibility of developing resistant stock

Other diseases Evidence of the familial incidence of Johne's disease (paratuberculosis) has been reported by Matthews (22) Among the 14 daughters of one sire the proportion contracting the disease was 86 per cent in those from another sire the incidence was only 15 per cent and in the progeny of a third, a son of the second the incidence was only 9.5 per cent. In the same herd there were three cows each of which had three daughters all affected with Johne's disease. While the evidence is not conclusive it seems probable that here as in so many other cases susceptibility is genetically determined

Some evidence of a familial basis for leukemia in cattle has been reported by Starr and Young (29) who studied 13 cases of the disease Drieux (6) and others cited by him also consider it hereditary but further studies seem desirable

The susceptibility of cattle to mycotic infection is also genetically determined as is recounted in Chapter III

THE HORSE

Opportunities to study genetic resistance to disease in the horse are decreasing rapidly as these words are being written Nevertheless two interesting examples are available for the record.

Encephalomyelitis When an outbreak of this disease struck the horses at an experiment station at Miles City Montana, in 1938 Lambert *et al.* (18) found that those of the *Nonius* breed (imported from Hungary) and crosses of the Nonius with others proved much more susceptible than the Belgians and Thoroughbreds which made up the majority of the stock

at the station Incidence of the disease in the two contrasting groups was as follows

	Horses	Affected per cent
In Nonius and crosses	3	58 1
All others	190	6 3

Since encephalomyelitis is transmitted by mosquitoes which carry the causative virus, it seems probable that all horses had equal chances of infection This is not a case in which draft horses differ from light ones in susceptibility since the 190 horses not of Nonius blood included 87 Belgians and 95 Thoroughbreds. *These two breeds did not differ significantly* in the proportions affected.

Mallenders Mallenders is a rather uncommon disease affecting the skin in the flexure of the carpus or knee In some ways it resembles psoriasis. According to Wussow and Hartwig (37) mallenders is confined almost exclusively to draft horses. Out of 192 affected stallions considered in their study 34 could be traced back to a common sire and 39 others to another common ancestor in four generations. They considered the disease hereditary and recessive in nature.

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Chapter VI

Resistant Birds

IN unhappy recognition of the inescapable fact that many farmers and most veterinarians regard domestic fowls as being intermediate in importance and interest between an earthworm and a goat, I shall try when writing this chapter to suppress an unbounded enthusiasm for my favorite species and to confine this brief survey to the salient facts. With its comparatively rapid rate of reproduction the fowl is one of the most suitable domestic animals with which to demonstrate the feasibility of reducing disease by developing resistant stock. Accomplishments in that field have already been discussed in some detail (Hutt, 11) but considerable new information has come to light since that review was written.

Pullorum disease. For many years bacillary white diarrhea of chicks was considered by some pathologists as one of the worst diseases with which the poultryman had to contend. With the modern trend toward replacing unpleasant words with happy euphemisms, the disease became known as pullorum disease after the organism which causes it, *Salmonella pullorum*, but afflicted chicks continue to have white diarrhea just as they did in the more primitive era.

After recognition of the fact that the causative bacterium is transmitted by hens that carry it through some of their eggs to the chicks and that it may then be spread to other chicks in the brooder it became standard practice to identify by the agglutination test the hens that carried the organism and to eliminate them from breeding flocks. Chicks thus hatched free of the disease should be raised without loss from *pullorum disease* The next step was to conduct extensive tests of breeding flocks in the attempt to eradicate the causa tive organism This has now become standard practice in most of the states in the United States.

A point overlooked in the earlier years of testing was the fact that White Leghorns are much more resistant to pul lorum disease than are heavy breeds such as Rhode Island Reds, Plymouth Rocks, and White Wyandottes. Figures for the first two years of testing in Connecticut and New Jersey as summarized (Table 10) from the various reports showed

T ble Hens (per cent) reacting t tests for *S pullorum* during the first tw years of testing in Connecticut and New Jersey showing comparatively low frequencies in Whit Leghorns

Breed	Connecticut		New Jersey	
	9 4– 9 5	9 5– 9 6	9 5– 9 6	9 6– 9 7
White Leghorns	4 5	8 4	3	4
Rhod Island Reds	9	9	5 7	0 4
Whit Wyandottes	6 6	3	7 9	9 6
Plymouth Rocks	4	7	4	4 4

From Hutt and Scholes in *Poultry Science* 94

that the proportion of reactors among the heavy breeds was from 5 to 8 times as high as in White Leghorns. A similar comparatively low incidence of reactors among White Leg horns was found in the first extensive tests made in Massachu setts, North Carolina, and British Columbia.

Experimental confirmation of the fact that Leghorns are more resistant than heavy breeds was obtained by Hutt and Scholes (20) who inoculated samples of the two classes with standard doses of the causative organism and tested others by exposure to natural infection by contact with inoculated chicks. In addition they discovered by testing white and colored sisters from sires heterozygous for the dominant white of White Leghorns, that White Leghorns owe their resistance not to their white color but to the fact that they are Leghorns. Other varieties of that breed should therefore be just as resistant as the Whites.

The feasibility of enhancing the natural resistance of White Leghorns by selective breeding was conclusively demonstrated by Roberts and Card (24) who tested successive generations of their chicks with standard oral doses of the pullorum organism and bred from the families showing the highest resistance In two strains of White Leghorns thus selected for only four years the proportions of chicks surviving the standard dose were 61 and 70 per cent but the corresponding figure for unselected controls given the same dose was only 28 per cent Another strain selected for nine years showed 74 per cent surviving that same dose

Crosses of the resistant stock with unselected controls produced offspring that were fully as resistant as the resistant parents (Fig 17) This suggests that strains thus made genetically resistant to pullorum disease may be doubly useful firstly as improved pure strains and, secondly for production of the strain-cross hybrids that are now so popular in the poultry industry When the F_1 generations from these crosses were mated back to resistant stock, resistance of the progeny was lowered somewhat, but it remained high in comparison with that of chicks from the other backcross namely F_1 birds mated to unselected controls (Fig 17)

One should not infer from what has been written thus far that chicks of the heavy breeds are hopelessly susceptible to pullorum disease By the simple process of natural exposure and selection, a good breeder in Maryland developed a re sistant strain of Rhode Island Reds. When it was tested by

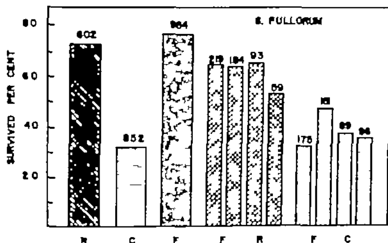


Figure 7 Survh al f chicks inoculated with *S pullorum* showing better results in the resistant strain (R) than in unselected controls (C), also the dominance of resistance in the F generation from th cross, R × C. In four different backcrosses of F × R, survival was consistently higher than in four backcrosses of F × C. Numbers of chicks tested are shown above the columns. (Drawn from data of Roberts and Card 1 Table 9 of *Illinois Agricultural Experiment Stati Bulletin* 4 9)

DeVolt *et al* (8) these birds were found to be almost as re sistant as the Leghorns of Roberts and Card, a number of which were tested at the same time. In the same experiment chicks from infected flocks proved much more resistant than chicks from flocks containing no reactors. Unfortunately none of the chicks in these trials were inoculated orally to

simulate natural exposure and the subcutaneous injections given caused unusually severe losses in all groups

Evidence from two sources showed that the resistant strains of Roberts and Card owed their biological superiority to their genes and not to any passive immunity transmitted from dams to chicks through the egg (1) in reciprocal crosses between resistant strains and (susceptible) controls, sires transmitted resistance just as well as dams—even slightly (but not significantly) better (2) hens found by agglutination tests to carry antibodies against *S pullorum* produced chicks that were no more resistant to the disease than were chicks from non reactors.

Up to the time of the first state wide tests, the results of which are given in Table 10, natural selection left the proportion of reactors in the White Leghorns of Connecticut and New Jersey at only 2.4 to 4 5 per cent. The results achieved by Roberts and Card indicate that a little selection on a family basis could have reduced that figure considerably

In the course of breeding fowls resistant to lymphomatosis at Cornell University Dr Cole and I have raised annually for some 25 years more than 2 500 White Leghorn pullets, which came each year from about 350 breeding females. These females have been tested regularly for pullorum disease but reactors have always been left in the breeding pens. In spite of this unorthodox practice the only serious losses experienced came in the earlier years of the work when through accidental chilling in the brooders, some pullorum disease was experienced. Any families losing a lot of chicks, whether from pullorum disease or from anything else have been eliminated from the breeding pens. Unfortunately in *the fourteenth year of our misconduct and in spite of* all our efforts to maintain a little infection no reactors whatever

could be found, and during the last 10 years only one reactor (and that a doubtful case) has been found among about 3,000 hens tested. Obviously selection for resistance ceased when the last reactor died. Having thus become clean (though not necessarily resistant) our White Leghorns have attained a state of impeccable respectability to which they are not quite entitled because of their shady past, their early defiance of orthodox precepts and the unconventional route by which their present status has been achieved. They like it.

Meanwhile the complete absence of natural selection in the regularly tested flocks of some New England states has resulted in the production there of stock that is admitted to be highly susceptible to pullorum disease New Hampshires sent to Ohio and to North Carolina were found to be much more susceptible to pullorum disease there than were the local chicks from infected flocks subjected to natural selection. Similarly Roberts (24) found Chia G1 chicks from infected areas in China to be relatively resistant, but Langshans from a pullorum free area were highly susceptible

Fowl typhoid. The feasibility of developing a stock highly resistant to *Salmonella gallinarum* has been demonstrated by Lambert (21) who inoculated chicks at 7 days of age and measured the resultant mortality for 3 weeks thereafter His standard dose of the organism was so strong that it regularly killed about 85 per cent of the unselected controls. In the fifth selected generation however only 9.4 per cent of his resistant strain succumbed to that same dose Reciprocal crosses between the resistant strain and the unselected controls showed that the males transmitted resistance just as well as did the females. This eliminated any likelihood that the resistant strain owed its resistance to passive immunity trans-

simulate natural exposure and the subcutaneous injections given caused unusually severe losses in all groups.

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	Resistant strain per cent	Susceptible strain per cent
Natural exposure, 1942	4.8	24.6
Natural exposure, 1943	1.1	6.0
Subcutaneous inoculation, 1942	56.8	57.5
Subcutaneous inoculation, 1943	73.2	71.7
Oral dosage, 1943 a	6.7	11.0
Oral dosage, 1943 b	8.6	44.4

It is clear that one strain was consistently more resistant than the other to natural exposure. This genetic difference was completely obliterated when the birds were inoculated subcutaneously and mortality was equally high in both strains. Oral dosage increased leucosis in the resistant stock but did not obscure the genetic difference between the two strains.

Admittedly natural exposure is difficult to control and it cannot be depended upon to administer a standard dose of any pathogen to each animal and to each successive generation. Sometimes a compromise works best, as with the oral doses of *S. pullorum* used by Roberts and Card. In that case the investigators followed the natural channel of infection but increased the number of organisms, and also made certain that all chicks were equally dosed. Unfortunately it is not always feasible, particularly with virus diseases, to standardize thus a dosage that simulates the natural kind of exposure.

Avian leucosis complex. This disease, which has had more different names than most others, is one of the worst problems with which the poultryman has to contend. It is responsible for 30 to 50 per cent of the mortality among young pullets during their first year of life.

Lymphomatosis is characterized by the accumulation of

mitted from the hens to their offspring through the eggs.

Leghorns are more resistant to *S. gallinarum* than are the heavy breeds (Smith 26) as might perhaps be expected from their greater resistance to *S. pullorum*.

The merits of natural exposure. Although the results of Lambert's selection were remarkable the work has been criticized, and not unjustly on several grounds. Fowl typhoid is ordinarily a disease of adult birds—not of young chicks. The intraperitoneal inoculations used by Lambert undoubtedly bypassed some of the normal defense mechanisms. Ordinarily birds have a chance to cope with invading organisms in their upper digestive and respiratory tracts before getting them in their bowels. One wonders whether or not the birds resistant to such artificial inoculation when chicks would have been equally resistant to natural infection when full grown, but this was apparently not investigated.

The comments in the previous paragraph are made, not to detract from the value of Lambert's demonstration, but rather to warn future investigators against forgetting that a laboratory experiment is one thing and application of the findings in practice is often quite another. It is highly desirable that there be further tests of the feasibility of breeding resistant stock. It is equally important to demonstrate that such resistance can be developed under conditions simulating natural exposure.

This point was nicely illustrated when Hersdorf *et al.* (10) tested two strains of White Leghorns by exposing samples of them to leucosis in three different ways. Some were left for natural exposure only, some were inoculated intraperitoneally with lymphomatous material, and others were dosed orally with the same material. In the two generations tested, subsequent mortality from leucosis was as follows:

	Resistant strain per cent	*Susceptible strain per cent*
Natural exposure, 1942	4.8	24.6
Natural exposure, 1943	1.1	6.0
Subcutaneous inoculation, 1942	56.8	61.5
Subcutaneous inoculation, 1943	73.2	71.7
Oral dosage, 1943 a	6.7	11.0
Oral dosage, 1943 b	8.6	44.4

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Lymphomatosis is characterized by the accumulation of

lymphocytes in the nerves, in various visceral organs, and occasionally in the iris. At one time all these different manifestations were considered to be caused by the same pathogenic organism a virus but some pathologists now believe that neural lymphomatosis and visceral lymphomatosis are caused by different viruses. To the poultryman neural lymphomatosis has been known for years as fowl paralysis be



Figure 8 A White Leghorn pullet showing typical position resulting from paralysis of the legs caused by neurolymphomatosis. (Courtesy Cornell University)

cause a common seat of the trouble is in the brachial and sciatic nerves, with resultant paralysis of a wing or leg (Fig 18) Other nerves however can be affected as well. A common manifestation of visceral lymphomatosis is the so-called "big liver disease" of the poultryman (Fig 19) and ovarian tumors are also frequent. All these different forms were at one time grouped by pathologists as different manifestations of the avian leucosis complex.

Various estimates have been made of the annual cost of

this disease to the poultry industry of the United States some of them run as high as $5,5,000,000 The disease does not strike all birds at a time but at any age after 6 weeks and up to two or three years of age lymphomatosis in one form or another may cause death. Most of the losses occur during the first year of life. Early attempts to control lymphomatosis by invoking the orthodox procedures of disinfection, discouraging visitors from other poultry farms, and



Figure 9. An enlarged liver showing nodular lymphomatosis, with normal liver for comparison. (Courtesy Cornell University)

importing disease free stock proved completely futile In most cases chicks from farms free of leucosis, when brought to premises where the disease had been present, suffered more severely than the birds that were replaced.

It was demonstrated by Asmundson and Biely (1) that some families are more susceptible to neur lymphomatosis than others. Similar differences among families can be seen in any pedigreed stock that is exposed. An experiment to determine the feasibility of breeding strains resistant to this

disease (and to others) was begun at Cornell University in 1935. The experiment differs somewhat from previous selection for resistance to disease in that the birds under test are given no intraperitoneal inoculations and no oral dosages of any kind but are left to contract the disease by whatever channels cause the usual natural exposure to the disease on infected premises. A high level of leucosis in the Cornell flocks at the beginning assured exposure adequate for differentiation of resistant and susceptible families. When it was discovered later that proximity to adult stock during the first 2 weeks after hatching increases the severity of exposure (18) it became routine practice to brood all chicks under test as near as possible to laying birds. Attendants walk regularly from old hens to chicks, but whether they carry the virus or whether it is wafted on the breeze is still a matter of conjecture All chicks are exposed as uniformly as is possible considering how little is known about the disease.

Viability is measured to 500 days of age Every bird that dies is examined to determine the cause of death and families showing the least leucosis are given preference as breeders. Nearly all of these examinations have been made by my colleague Dr R K. Cole who has collaborated in this experiment almost from its inception except for a four year interlude during the Second World War As the work has progressed, it has been found profitable to concentrate on using sires that have proven their ability to transmit a high degree of resistance to their offspring When it became evident that a limiting factor in the selection program was a shortage of such sires, a system of multiple shifts for testing cockerels was devised (17) and thereafter more rapid progress was made

For the purposes of this experiment the usual washing and disinfecting of premises have been dispensed with but

quarters for chicks, for growing stock, and for adult birds have been kept reasonably clean. This cavalier attitude toward disinfection at first engendered considerable consternation among our colleagues, to some of whom from long addiction, carbolic acid was more fragrant than Chanel No. 5 No special precautions have been taken to prevent bacteria viruses, or anything else from getting around on the boots or clothing of visitors and attendants. The latter have gone regularly from hen pens to chicks without stepping into any pans of disinfectant such as are commonly believed by the faithful to give protection against the transfer of pathogenic organisms.

From the outset the experiment differed in one important aspect from any previous attempt to breed resistant stock. The object of the experiment was to determine the feasibility of breeding a strain so resistant to leucosis that losses from that disease would be reduced to an insignificant level. It was recognized however that there would be no point in demonstrating such a procedure to be feasible unless it could be shown also that these resistant birds could lay well and be satisfactory in such other characteristics of economic importance as body size egg size and the ability to reproduce Accordingly all these objectives as well as some others are considered in the selection program. This makes the selection much more difficult because it is harder to find families that excel in each of several qualities than to find a family that is superior in only one of them Many a male that produced daughters resistant to leucosis was discarded because these same daughters did not lay enough eggs to qualify

Two strains of White Leghorns have thus been bred for resistance to lymphomatosis but at the same time a third has been bred for increasing susceptibility to that disease. Reports of their performance have been given in detail else

where (12 13 15 16 19) The record of these three strains over a period of 20 years is shown in Fig 20 Although that figure shows the level of mortality from leucosis in 1935 to be only 15 per cent the incidence of the disease was undoubt

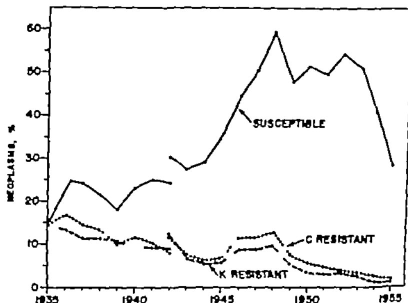


Figure 20. Mortality in White Leghorns from neoplasms (nearly all lymphomatosis) showing the differentiation by breedi g of two highly resistant strains nd one highly susceptible. Higher dots for each strai in 1942 pply to birds severely exposed, lower dots to those exposed lightly (see context). Lines re smoothed by use of a 3-year moving average except for terminal points. (From data f Hutt and Cole, Cornell University)

edly considerably higher In those early days of the experiment, mortality from coccidiosis and other causes prevented many a pullet from demonstrating its susceptibility to leu cosis, but better management soon gave more birds a chance to die of the latter disease From 1935 to 1942 half of the chicks had only a relatively mild exposure, as we later dis-

covered because they were brooded farther from adult birds than their fellows (18) but after that date all birds were given the severest natural exposure that we could provide. Had they all suffered that same degree of exposure from the outset, it is probable that the mortality from leucosis in 1935 would have been twice as high as is indicated in Fig 20

As birds of all three strains have been intermingled in the brooders and flocks throughout the experiment, it is evident that the difference between the two resistant strains and the other one in susceptibility to lymphomatosis is the result of selection and not of any environmental influence. It is clear (Fig 20) that mortality from neoplasms, 90 to 95 per cent of which were cases of lymphomatosis, was gradually reduced in the two resistant lines until by 1955 it was negligible. At the same time selection in the opposite direction made the third strain so susceptible that in several years more than half of the pullets succumbed to this disease.

The effect of this sort of breeding on the economic value of the resistant strains is indicated by the record for the C Resistant line (Fig 21) Mortality from all causes dropped from 67 per cent in 1935 to 15 5 per cent for the birds hatched 20 years later At the same time egg production to 500 days of age was raised from 177 to 204 eggs. Because of these improvements in both viability and productivity the production index, which is a measure of the economic value of a flock, rose from 90 to 187 This is the average number of eggs laid *per pullet housed* at 5 months of age Moreover average definitive egg weight for the hens of 1955 was 61 5 grams, a figure higher by 13 per cent than the corresponding egg weight of their ancestors in 1935 These levels of performance indicate that the birds of the resistant strains were economically satisfactory in most respects.

In order to determine how our birds compared with other

highly improved strains particularly with respect to viability random samples of the resistant stock were entered in the Central New York State Random Sample Test for three consecutive years, 1953 1954 1955 In that test 50 female

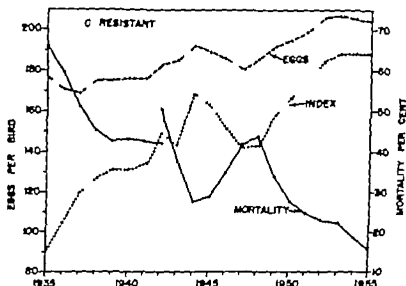


Figure 5 Effects of selection on performance of the C Resistant line showing reduction of mortality increase in number of eggs laid per surviving bird, and rise in production index. All lines are smoothed by use of a 5 year moving average except for terminal points. *(From* data of Hutt and Cole, Cornell University)

chicks were started per entry each year Unpedigreed samples of eggs were turned over to the manager of the laying trial, after which we the breeders, *had no supervision over the* birds. Post mortem examinations were made by veterinarians in another laboratory where all casualties in these tests were handled To cut a long story short, when the records for three years *had been summarized it was found that among*

15 strains which had been entered for all three years (Table 11) the Cornell resistant stock ranked lowest in mortality from all causes lowest in mortality from neoplasms (mostly leucosis) and second to the highest in income per chick started. Other strains laid somewhat better than ours but returned a lower profit per chick because fewer of them sur vived to 500 days of age

Table 1 Three year-average performances in the New York Random Sample Test

	Highest	Average of 25 entries	Cornell resistant stock
Mortality -500 days			
from all causes, per cent	39 7	25	8 3
from neoplasms, per cent	2 8	1 6	4.0
Eggs per pullet housed, number	2	9 7	208.8
Income per chick started, dollars	46	.05	2.4

From 3 *Year Averag Report* *f 4th 5th d 6th New York Random Sample Poultry Test* 957

These results show that it is entirely possible by selective breeding to develop stock so resistant to leucosis that mortal ity from that disease under conditions of fairly severe ex posure can be reduced to an almost negligible level. This can be done without sacrificing the ability to lay and to be profitable. In fact, the records in the New York Random Sample Tests have shown that the dollars-and-cents return per chick started is probably influenced more by the level of mortality in the different entries than by any other factor

The improvement of viability in the resistant strains (Fig 21) should not be credited entirely to their ability to with stand leucosis. Over the years the stock has encountered

laryngotracheitis cholera, Newcastle disease, bronchitis, blue comb disease coryza, pullorum disease and most of the other ailments that can beset domestic fowls in our latitude Al ways the most resistant families, when otherwise satisfactory have been selected to produce the next generation. It is not unreasonable to suppose that the cumulative effects of such selection have helped to raise the resistance of these strains to other diseases as well as to the leucosis against which our efforts were concentrated.

The fact that this experiment has been continued for more than two decades does not mean that it takes 20 years to breed hens resistant to leucosis Improvement would un doubtedly have been more rapid if it had been recognized *earlier that the chief factor limiting progress was a shortage* of superior sires. If greater numbers of males could have been tested from the outset, either by using more pens for single male matings or through the system of multiple shifts (which did not go into effect until 1942) the two resistant strains should have improved at a faster rate As the average number of our single male breeding pens per year after 1942 was only 10 5 for one strain and 8 2 for the other it is clear that other poultry breeders, even those operating on a com *paratively small scale can make their own strains genetically* resistant if they use proper procedures. Many of them are now doing so

During the course of this work considerable evidence was found of the influence of environment on mortality from leucosis. Both heredity and management have important roles in control of the disease and these are discussed in Chapter IX

Blue comb or monocytosis This disease, sometimes called pullet disease, commonly strikes young pullets when they

have just begun laying or before, although it may occur at later ages. It is rather difficult to combat, and at various times the remedies prescribed have included molasses, muriate of potash, and, of course the inevitable antibiotic. In afflicted flocks some of the birds have dark combs and appear slug gish, on post mortem examination they are typically dehy drated and show local ischemia, sometimes even the whole pectoralis muscle being affected The disease which is now thought to be caused by a virus, usually interrupts laying for a period of several weeks, but the mortality may be relatively light.

Cole (6) has shown that susceptibility to blue comb is genetically determined, and this fact has since been con firmed by Moultrie *et al.* (23) In Cole's birds, which were afflicted on the rearing range at 9 to 17 weeks of age the mortality in four different strains or stocks of Leghorn pul lets, all intermingled, was as follows

	Birds tested	Died of blue comb per cent
In Line C	986	7.40
In Line K	1 512	0 99
In crosses, C × K	358	3.25
In Line S	221	0.00

As these figures show there were significant differences among the three strains in susceptibility to blue comb. The strains did not differ in concurrent mortality from other causes except that Line S lost 10 times as many birds from lymphomatosis as all the rest put together This it was ex pected *to do for it is our line bred for susceptibility to that* disease.

The probability that susceptibility to blue comb is poly genic, and not a simple Mendelian character is shown by the

fact that birds from the cross of susceptible (C) × resistant (K) lines suffered losses almost exactly intermediate between those in the two parental stocks. Apart from the strain differences highly significant variations in susceptibility were found among the families of different sires within Strain C. Some of the sires lost no daughters whatever but one lost as many as 47 per cent of his daughters. Two of that sire's sons, in turn each lost about 35 per cent of their daughters during the outbreak. Similar differences, many of them highly significant, were reported by Moultrie *et al.* among 16 sire families exposed to blue comb. Among these the losses ranged from 0 to 36 per cent

Although it is useful to demonstrate by means of differences among strains and families that susceptibility to some disease is genetic it is much more important to show whether or not the incidence of that disease can be effectively reduced by selection against it. A good control for such an experiment is a second strain selected for greater susceptibility Dr Cole and I undertook to select for both resistance and susceptibility and to that end mated our most resistant families for one line and our most susceptible ones for the other Unfortunately our best laid plans went agley we have not seen even a smitch of blue comb in the seven years since our first experience with it.

This illustrates one of the difficulties in attempting to breed for resistance to disease when one is dependent upon natural exposure On the other hand, no pathologist can yet give us the blue-comb virus in convenient little bottles from which we can provide standard doses to the birds we wish to test.

Resistance to coccidia. Good evidence of genetic differences in resistance to coccidia was found by Rosenberg *et al.* (25)

who demonstrated clearly the feasibility of developing stock highly resistant to that protozoan parasite. Working with *Eimeria tenella* and feeding large standard doses of sporulated oocysts to chicks at 14 or 28 days of age, they differentiated in only three generations of selection two strains, in one of which 88 per cent of the chicks tested could withstand the standard dosage, whereas in the other line only 45 per cent could do so After 3 to 5 generations of selection, reciprocal crosses were made between the resistant and susceptible strains with results as shown in Fig 22 Both in matings with untested cockerels and in those with proven sires, matings *inter se* of the resistant stock produced highly re

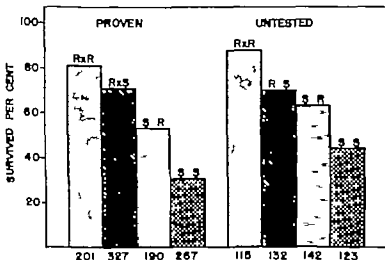


Figure 22 Survival rates for chicks uniformly dosed with *Eimeria tenella* showing good results in the resistant line (R), low resistance in the susceptible line (S), and intermediate resistance in the F generations from reciprocal crosses between R and S Columns on the left pertain to offspring of proven sires, but, as the columns th right show R and S males previously untested also transmitted the degree of resistance characteristic of their strains. Numbers of chicks tested are shown below the columns. (After Rosenberg *et al.* in *Poultry Science* 954.)

sistant offspring and susceptible families mated *inter se* yielded highly susceptible progeny Crosses of resistant × susceptible produced chicks that were intermediate between the two parent stocks The fact that the trials involving the untested cockerels yielded results much like those with proven sires shows that the resistance had been firmly established by the few generations of selection as a strain characteristic. The slightly higher viability shown by the crosses from resistant sires than by those from resistant dams suggests that sex linked genes are involved but other data refuted that possibility It is worth noting, however that these same discrepancies in reciprocal crosses disprove any possibility that the resistance demonstrated could have resulted from passive immunity transmitted by the resistant dams to their progeny In both cases dams of the resistant strain appeared to produce more susceptible offspring than did sires of the resistant strain but it is probable that the differences are not significant.

Poultrymen have long since learned that the extreme sanitation once considered a preventive of infection with coccidia could, in many cases, cause tragedy when birds that had been kept free up to 5 months of age then became infected. It is now recognized that much better control is gained by exposing the chicks to relatively small doses at early ages, so that they can develop immunity or resistance to the coccidia The evidence of Rosenberg *et al.* (25) has been confirmed in similar experiments by Champion (4) Together they suggest that a little selection might go a long way in reducing losses from what is sometimes a costly kind of parasitism

Resistance to nematode worms Using standard infective doses of embryonated eggs of the nematode *Ascaridia lineata* Ackert *et al* (1) observed that that parasite thrived better in the White Leghorns than in the heavier breeds, such as

Rhode Island Reds and Plymouth Rocks, which were tested at the same time Confirmatory evidence was reported by Morgan and Wilson (22) who found that among different breeds maintained at a laying test under fairly uniform con ditions the cecal worm *Heterakis gallinae* was more numer ous in White Leghorns than in Rhode Island Reds and White Wyandottes.

Further evidence of genetic susceptibility to nematode parasites is desirable. The cases cited provide the only in stance among several comparisons in which the Leghorns have been found less able to cope with stress factors of various kinds than are the heavy breeds. In resistance to bacterial infection and in resistance to dietary inadequacies of various kinds the Leghorns have been found to be supe rior It would be interesting to know why their biological superiority in some respects should make them less qualified to cope with these worms. Evidence of geneti differences within any of the breeds mentioned has not yet been adduced

Resistance to aspergillosis Among five different strains of White Leghorns exposed under uniform conditions to an outbreak of infection by the mold *Aspergillus fumigatus* highly significant differences in susceptibility to the infection were found by Brooksbank and Austwick (9) In two strains mortality from aspergillosis was 31 and 50 per cent but in three others, one of which was represented by no less than 148 chicks, there were no losses whatever from this disease Similar differences were found in the Rhode Island Reds, one strain of which lost 74 per cent from the fungous infec tion, while the other with 167 chicks under the unsought test, lost not a single one from aspergillosis

While these highly significant differences between strains in both breeds show clearly that genes influence resistance and susceptibility to infection with *A fumigatus* it would

be interesting to have the genetic influence tested further by selection experiments. This case is of particular interest because, along with Hansson's mycotic infection in cattle (considered in Chapter III) it extends the range of pathogenic organisms affecting domestic animals to which genetic susceptibility has been demonstrated. Fortunately fungous infections are not so common as some other afflictions but it is to be hoped that further evidence of genetic susceptibility to them may be sought.

Miscellanea. Highly significant differences in susceptibility to osteopetrosis were found by Coles and Bronkhorst (7) among families of White Leghorns. Affected birds show extreme thickening and hardening of the long bones and others, a condition resembling the osteopetrosis or marble bones of man. It is not common.

Strains and families differ also in susceptibility to respiratory infections, but the feasibility of producing highly resistant strains by deliberate selection has not yet been demonstrated. The role of the genes in determining such resistance is shown by recent conclusive evidence reported by Goodwin *et al.* (9) that the F_1 generations from crosses between strains are more resistant to respiratory disease than the parent strains that are crossed. Such crosses are already popular because their hybrid vigor often results in better egg production or better growth than can be had with pure strains. The fact that hybrid vigor is also expressed as superior resistance to respiratory infection should make the strain crosses doubly valuable in the many areas where exposure to such infection is inevitable. It does not follow that hybrid vigor increases resistance to other diseases. In strain crosses that excelled the parental strains in several different measures of performance thus indicating a considerable degree of

heterosis, mortality from neoplasms was actually slightly higher than in the pure strains (14)

Fowls differ in susceptibility to spontaneous tumors other than leucosis but fortunately these are not common in younger birds. With only four generations of selection for susceptibility Cole (5) developed a strain of Leghorns in which over 77 per cent succumbed to inoculation with a transmissible sarcoma. At the same time three generations of selection in the opposite direction produced a strain so resistant that only 12 5 per cent of the inoculated birds succumbed.

Summary The evidence reviewed in this chapter shows that fowls differ genetically in ability to resist invasion by bacteria, viruses, fungi, parasitic protozoa, and worms. Every effort to enhance resistance by selection has been successful The feasibility has been demonstrated of combining resistance to disease (leucosis) with high productivity to produce stock of superior economic value These facts suggest that genetic resistance to disease in the fowl should be utilized to a much greater extent than it has been They also suggest, since no one species has a monopoly on biological fitness, that probably other domestic animals also carry valuable genes for resistance to disease that have not been recognized as yet but which could be utilized to advantage.

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Chapter VII

Aberrant Metabolism

DISEASES resulting from genetic defects in the normal processes for utilizing nutrients in the diet are sufficiently numerous and important to warrant a special chapter The range of variation in this field runs all the way from lethal mutations, through various physiological handicaps, to economically important genetic differences in ability to convert feed into meat, milk, eggs, and other things for which man keeps animals under domestication

One of the most familiar examples of such defects is the inability of some seedlings to manufacture chlorophyll In maize and in many other plants, this abnormality is known to be caused by a simple recessive mutation in the homozygous state Similar variations have been studied in *Neurospora* the bread mold. In that organism simple mutations at various points in complex chains of reactions have been shown to prevent the synthesis of many essential amino acids and vitamins. Genetic variations in metabolism are also known in various bacteria.

In higher animals genetic defects of metabolism are more often concerned with blocks whereby the transformation of complex proteins, fats, and carbohydrates to the simple forms in which their constituents are utilized is stopped at some

critical point. There are also mutations that cause genetic variations in the amounts of certain essential nutrients required for normal function

Aberrant metabolism in man A few examples from our own species will exemplify the kind of disease that results from genetically aberrant metabolism. Three of them prevent the normal breakdown of the amino acids, phenylalanine and tyrosine If the block occurs at one point affected persons excrete phenylpyruvic acid in the urine whereas normal people utilize that substance by breaking it down to others less complex. All people afflicted with this defect of metabolism are feeble-minded none rating higher than an imbecile or an idiot.

Another block at a different point in the breakdown of phenylalanine and tyrosine causes albinism. This is not necessarily a serious abnormality but in some environments it is a distinct handicap At a third point in the same chain of metabolism another block causes affected persons to excrete homogentisic acid also called alcapton These people lack the enzyme necessary to break that substance down to carbon dioxide and water They are said to have alcaptonuria and *their peculiarity can be recognized by the fact that their* urine turns black when exposed to air The condition is not serious, although there are some indications that it may increase susceptibility to arthritis.

An abnormality in the metabolism of fats whereby sphingomyelin is accumulated in the body tissues is responsible for the condition known as amaurotic idiocy or Tay Sachs disease. Infantile amaurotic idiocy is usually lethal before three years of age. *It is a simple recessive character* Another variation of fat metabolism is responsible for the accumulation of cholesterol in excessively high amounts in the

blood. Persons afflicted with hypercholesterolemia are more subject than others to arteriosclerosis and coronary disease Some of them show deposits of cholesterol in the skin and eye-lids, a condition known as xanthomatosis Hypercholesterolemia is apparently caused by a dominant gene that acts with varying degrees of severity in persons heterozygous for it and has more extreme effects in homozygotes.

Diabetes is a familiar example of a genetically aberrant metabolism of carbohydrates. Another is galactosemia, caused by deficiency of an enzyme that ordinarily helps to break down galactose. The defect is hereditary and apparently lethal to babies homozygous for the causative gene

All of these abnormalities of human metabolism are likely to occur in domestic mammals, but apparently the only one of those mentioned above that has been recognized thus far is diabetes, a not-uncommon disease in dogs.

Porphyria. This condition characterized by the accumulation of porphyrin in the blood its deposition in the bones, teeth, and other tissues and its excretion in the urine is a simple recessive defect of protein metabolism in cattle and swine. It can be recognized by the pink teeth of affected animals and by the fact that the urine turns reddish brown One effect of excessive porphyrin in the blood is to make the animals extremely sensitive to sunlight. On areas of the skin not protected by hair exposure to the sun causes blisters that eventually become deep ulcers and may leave bad scars. These are found around the eyes and nostrils and on the mid-line of the back where the hair parts

A study of Shorthorns in South Africa afflicted with porphyria showed it to be a simple recessive character (Fourie, 4). The condition provides a good example of the way in which heredity and environment can interact. Af

fected cattle exposed to sunlight developed severe abscesses in all parts not covered by hair However in one such animal that for 10 years was kept indoors during the day and allowed out in its paddock only at night health was perfectly normal and the animal was destroyed at 18 years of age only because its teeth had become bad (5)

Porphyria has also been found in cattle and swine in Denmark (10) and in Tamworth pigs in New Zealand (5)

Excess of phylloerythrin Hancock (6) has described an interesting kind of photosensitization found in Southdown sheep and caused by a simple recessive mutation. Lambs homozygous for this defect have some malfunction of the



Figure 13 Photosensitized sheep with drooping ear swollen lips "Roman nose, and swollen eyelids showing lesions on the upper one (Courtesy of N T Clare, Ruakura Animal Health Research Station, New Zealand.)

liver whereby it fails to excrete phylloerythrin a product of the digestion of chlorophyll Normally it is absorbed from the digestive tract and eliminated in the bile, but in the defective lambs phylloerythrin gets into the peripheral circulation and in unprotected areas of the skin is activated on exposure to light (Clare 2)

Afflicted lambs do not show lesions until they begin to graze at about 5 to 7 weeks. The severity varies according to the milk supply from the ewe and the intensity of the light Bad cases develop eczema over the face and ears (Fig 25) and, if the lambs are left outdoors, death ensues 2 to 5 weeks after the first symptoms. If the lambs are brought indoors however and sheltered from the sun they learn to graze only at night, to seek shelter during the day and thus to live in spite of their physiological peculiarity

A remarkable feature of this study was the series of matings (Table 12) by which Hancock showed that this condi-

Tabl 2. Results from various matings of sheep showing that inability to excrete phylloerythrin is simple recessive mutation

Parents		Offspring	
Nature of mating	Genotypes	Normal	Affected
Homozygous normal × affected	$PP \times pp$	74	0
Heterozygotes × affected	$Pp \times pp$	8	6
Affected × affected	$pp \times pp$	0	4
Affected × sheep from (normal × heterozygote)	$pp \times (PP \times Pp)$	7	5

From data of Hancock in *New Zealand J urnal of Scienc d Technology* 950

tion is caused by a simple recessive gene p in the homozygous state The proced re was routine for any genetic analysis, and the numbers of animals involved were not remarkable

for studies with small rodents, but they were unusual for large domestic animals. The backcross ratio of 18 : 16 and the fact that all 14 lambs from parents both of which were afflicted showed the defect provided good proof of the simple genetic basis.

Although this condition has thus far been reported only in sheep, it should be watched for in other animals. Most photosensitization is caused, or aggravated, by certain plants which contain sensitizing pigments. It is quite possible that, apart entirely from the two genetic defects just discussed, animals differ genetically in ability to excrete such pigments.

Purine metabolism of Dalmatian dogs. An interesting case of aberrant metabolism is found in Dalmatians. Although the condition does not cause disease, it affords an excellent example of the way in which a simple recessive mutation can affect a physiological process.

In man and in chimpanzees the purines are broken down to uric acid, but in rodents, carnivores, and many other mammals uric acid is broken down still further by the enzyme uricase, which converts it to allantoin. In most dogs that substance is the chief end product of purine metabolism. Dalmatians, however, excrete relatively high amounts of uric acid and apparently do not break any of it down to allantoin, although they do have the enzyme uricase. The amount of uric acid excreted daily per kilogram of body weight was found by Trimble and Keeler (20) to vary from 4 to 10 milligrams in ordinary dogs but to be 28 milligrams or more in Dalmatians. Their genetic evidence, together with the earlier studies of Onslow (18), shows that the difference is caused by a simple recessive autosomal mutation and that it is independent of the spotting characteristic of Dalmatians.

This poses the interesting question Where did the breed get its peculiar physiological trait? As that variation can be detected only by chemical analysis it could not have been deliberately sought in the formation of the breed, as was done with the spotting that is typical of Dalmatians. Although its origin is a mystery the case is of interest because what is apparently normal for the breed, namely the excretion of relatively large amounts of uric acid, is abnormal for the species. So far as is known it has no harmful effects.

Yellow fat in sheep Some sheep form yellow fat instead of the white fat that is normal for the species. According to evidence found by Zóphóniasson, as reported by Mohr and Castle (14) animals producing yellow fat differ from others by a simple recessive mutation The same situation is known in rabbits. The chemical basis for the difference between yellow fat and white fat in sheep has not been worked out, but it probably results from a genetic difference in the metabolism of carotinoid pigments.

Sheep with yellow fat are apparently normal and just as good in every way as sheep with white fat—except when their meat is put on sale Zóphóniasson stated that the abnormal color made the meat unsalable in a market where the people were accustomed only to white fat in sheep. Thus far the mutation has been reported only from Iceland.

Genetic differences in utilization of riboflavin. Normally the riboflavin needed for the development of chick embryos and the hatching of chicks is deposited in eggs by the hens that lay them. To ensure an adequate supply for the hen and a surplus to go in the egg, most diets for breeding hens now include about 1 300 micrograms of riboflavin per pound of feed.

Maw (13) has described an interesting deviation from the normal process. It was recognized because some White Leg horns produced fertile eggs in which every embryo died after 10 to 14 days of incubation. Analyses showed the eggs to be abnormally low in riboflavin in spite of the fact that the hens which produced them were getting an abundance of that substance in their diet. Treatment of these fowls with extra doses of riboflavin did not improve the hatchability of their eggs, but when amounts of riboflavin varying from 25 to 200 micrograms were injected directly into the de ficient eggs at 9 to 11 days of incubation, normal development ensued and the chicks hatched. Clearly these abnormal hens were unable to transfer riboflavin from their diet to their eggs as other hens do

Females of the F_1 generation thus artificially produced were found to lay eggs having a normal content of riboflavin but in the F_2 generation the ratio of normal hens to defective ones was 67 21 and a backcross of F_1 ♂ × defective ♀♀ yielded a ratio of 3 normal 5 defective Since these were in almost perfect agreement with the 3 1 and 1 1 ratios ex pected with segregation of a simple recessive character it seems clear that the abnormal hens were homozygous for a recessive gene which, in some unknown way prevented them from putting enough riboflavin in their eggs to permit normal embryonic development.

Other genes with lesser effects apparently determine how much riboflavin a hatched chick needs for normal growth and survival. By testing chicks on a diet deficient in riboflavin and selecting for six generations, Lamoreux and Hutt (12) differentiated two strains of White Leghorns, one compara tively resistant to the deficient diet, the other more suscepti ble than unselected controls. Resistance was shown not only by better survival on that diet to 5 weeks of age but also by significantly better growth

When chicks of the resistant and susceptible strains were compared on a diet containing ample riboflavin they did not differ significantly in their rates of growth It was considered, therefore, that the genetic differences between them were concerned specifically with the utilization of riboflavin.

Special requirement of riboflavin by black chick embryos Some years ago a large hatchery reported to the writer that among the black (female) chicks from its sex linked cross



Figure 24 Bare backs resulting from the abnormally high requirement of riboflavin by black chick embryos. (From H tt in *Genetic* 95)

(Barred Rock ♀♀ × Rhode Island Red ♂♂) there were always a few showing bare backs or sparse down on the back (Fig. 24) These defects made the chicks unsalable. As the cross was made primarily to produce these black females, which commanded a much higher price than their brothers, it was highly desirable to eliminate the barebacked chicks if that could be done.

Study of this problem (9) brought some interesting facts to light. The usual test matings that reveal genetic variations showed no evidence whatever that the bareback condition segregated as a genetic mutation Nevertheless, it was associated with black down. Among chicks from four different matings, each of which produced chicks of four different colors, the incidence of barebacked chicks was as follows

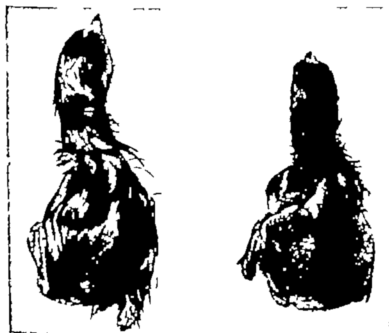
	Number	*Barebacked per cent*
In blacks	103	35.9
In silvers and golds	219	0.0
In barred	94	6.4

The comparative scarcity of barebacked chicks among the barred chicks agreed with the hatchery's report that the defect was rarely found in the males from their sex linked cross. All those males are barred In our experiments the few bare backed, barred chicks that were found came only from hens that had once been barebacked chicks.

Careful measurements showed that black chicks have down feathers significantly shorter than those of their full siblings that were silver or gold or barred. It seemed probable therefore that the bare back in black chicks is an extreme and visible stage of some condition which interferes with full development of the black down In most black chicks that interference merely shortens the down, an effect which is not recognized unless one makes a special examination for it.

Eventually it was found that for every barebacked chick that manages to hatch from this cross there are about five more that die in the last week of incubation In other words, the loss to the hatcheryman was five times as great as he had thought Nor was it restricted to one hatchery During the course of the study several others that were making the same sex linked cross presented the same problem

Among the black chicks that failed to hatch many showed not only the same sparse down found in some of those that did hatch but also peculiar granular or clubbed down (Fig 25) This had previously been shown to be as-



Figur 5. The amount of riboflavin in the eggs in which these chicks developed was adequate for the barred male on the left because its production of melanin was reduced by the gene for barring. It was not enough to let the no barred female on the right grow coat of solid black down, and she died at 20 days f incubation showing the sparse, clubbed down that indicates deficiency f ribofl vin. (From Hutt in *Genetics* 93)

sociated with a deficiency of riboflavin in the diet of the hen that produces such embryos. However since the diets fed to breeding flocks contain an extra margin of riboflavin over the actual requirements of most birds, it hardly seemed possible that any deficiency of riboflavin could be responsible

for the deaths of these embryos or for the barebacked chicks.

This problem was cleared up by Bernier and Cooney (1) after they observed that when diets were deficient in riboflavin mortality fell more heavily upon black embryos than on others. Controlled experiments in which the two types were produced by the same dam showed clearly that on diets somewhat deficient in riboflavin, black embryos experienced higher mortality during incubation than their full siblings of other colors. When alternate eggs from these same matings were given a supplement of 220 micrograms of riboflavin (in the air cell) embryonic mortality was decreased and hatchability raised correspondingly but the chicks not black still hatched better than the black ones (Table 13)

Table 13 Hatchability (percentage of fertile eggs) of black chicks and their full siblings not black, showing handicap of the former and improved hatch of both when extra riboflavin was supplied

Breed of dam	Eggs deficient in riboflavin		Additional 220 µg riboflavin per egg	
	Black chicks	Chicks not black	Black chicks	Chicks not black
Black Cornish	8.4	80.9	51.8	63
White Cornish	31.6	5 3	7 4	87.9
Australorp	60 6	—	85.7	—

From data of Bernier and Cooney in Sect n *Papers of Tenth World Poultry Congress* 1954

These studies show that there is some peculiar antagonism between the production of melanin and the utilization of riboflavin in these black chicks. The comparatively high hatchability of the black Australorps from Bernier's eggs deficient in riboflavin is attributable to the fact that the ventral surface in such chicks is predominantly white hence the amount of melanin produced by an Australorp embryo

is less than in embryos entirely black. Similarly addition of the gene for barring to chicks that would otherwise be black reduces the production of melanin by the barred males from the sex-linked cross described earlier and thus spares them from the prenatal mortality and bare backs that beset their all-black sisters.

Exact requirements have not yet been worked out, but it would appear that black embryos need several times as much riboflavin as others if they are to develop normally and to hatch. *It remains for some biochemist to investigate the exact* nature of the special requirement of riboflavin for formation of melanin. Whatever it is, it cost one hatchery about $178,000 in a decade because of the lethal action of the gene *E*, which causes extension of melanin throughout the plumage to make the chicks black (9)

Genetic differences in utilization of thiamine Under ordinary conditions domestic fowls are not likely to show symptoms of thiamine deficiency since most diets contain an abundance of that vitamin. We must not forget, however that it was Eijkman's recognition of polyneuritis in his chickens fed garbage from the hospital of the Javanese prison where he was medical officer that led him to conduct experiments in which some birds received only polished rice while others got rice with the outer layer left upon it. Out of these grew his discovery that the outer layer contained something which *could prevent, not only polyneuritis in his fowls, but* also beriberi in his patients. We now know that something as thiamine, or vitamin B_1

Birds of heavy breeds like Rhode Island Reds Plymouth Rocks, and White Wyandottes will show symptoms of a deficiency of thiamine early and few of them can live longer than 3 weeks on a deficient diet. In contrast, Nichita and

Iftimesco (15) found that their Leghorns could take such deficient diets without any sign of polyneuritis for as much as 5 months or more. Further studies by Lamoreux and Hutt (11) confirmed the fact that Leghorns are much more resistant to a deficiency of thiamine than are the heavy breeds. Their experiments were done with chicks to eliminate any possibility of the results being affected by difference in size between adults of the breeds compared Whether the chicks were started on a deficient diet at hatching, at 2 weeks of age, or at 5 weeks of age in every case the White Leghorns were less affected than the heavy breeds.

A little later it was shown by Scrimshaw *et al* (19) that White Leghorns put 60 to 66 per cent more thiamine in their eggs than do the heavy breeds, when all are maintained on the same diet. This has recently been confirmed by Howes and Hutt (8) who used a different method of assay and tested eggs from several different strains of each breed. They found the average amount of thiamine per hundred grams of yolk to be as follows

	Strains number	*Thiamine micrograms*
White Leghorns	13	198
Rhode Island Reds	5	138
Barred Plymouth Rocks	8	184
New Hampshires	4	146

Differences among the heavy breeds or among the 13 strains of White Leghorns were not significant, but the difference between the White Leghorns as a group and the others was highly significant. Since all these birds received the same diet, it is assumed that the White Leghorns had more unused thiamine left above their requirements and that the higher level of that vitamin in the blood resulted in its greater deposition in the egg

From all the evidence it is clear that Leghorns manage to get along on considerably less thiamine than is needed by birds of the heavy breeds The reasons for that difference are still unknown Similar differences in thiamine requirements have been found among different strains of laboratory rats.



Figure 26 The biologically efficient White Leghorn. I comparison with heavier breeds she is more resistant to pullorum disease, typhoid, encephalomalacia, and extreme heat and requires less manganese, thiamine, and vitami D How and why she does it ha e yet to be determined. (Courtesy Cornell University)

The efficient Leghorn While we are about it, it may be well to point out that Leghorns (Fig 26) are biologically superior to the heavy breeds in several distinctly different ways. Their greater resistance to pullorum disease and to fowl typhoid was discussed in the previous chapter and their lower require

ment of manganese for bone formation was cited in Chapter III

Leghorns also need less vitamin D than do the heavy breeds. Olsson's studies (17) indicated that Rhode Island Red chicks require about 2 7 times as much vitamin D for normal development of the skeleton as do White Leghorn chicks. When vitamin D was not supplied in the diet the Rhode Island Reds required about 3 6 times as much irradiation with ultraviolet light to meet their vitamin D requirements as did the Leghorns The fact that these differences were consistent and significant in all comparisons of the two breeds is remarkable because the representatives of the two did not differ significantly in the rate of growth at the time. Earlier Olsson (16) had found that some White Leghorn hens are able to maintain egg production and to reproduce well without any supplement of vitamin D while others cannot do so

White Leghorns are also resistant to encephalomalacia which is generally considered to be caused by a deficiency of vitamin E. On an experimental diet which caused a rather high incidence of encephalomalacia, Howes and Hutt (4) found in several comparisons, that White Leghorns were much less affected than were Rhode Island Reds and Barred Plymouth Rocks. The differences were significant and consistent but there was no difference between White Leghorns of different strains in ability to withstand the deficient diet.

All of these differences in nutritional requirements between Leghorns and heavy breeds indicate genetic differences in the metabolism of different nutrients. It would be interesting to know by what process of selection these physiological differences between breeds have arisen. None of them are characteristics for which selection could consciously have been made by those who set up the Leghorn breed

Other genetic differences in metabolism All of the cases cited hitherto in this chapter deal with genetic differences affecting the metabolism of some specific substance. There are also genetic variations in the efficiency with which the diet as a whole is utilized These are commonly reflected in more rapid growth higher production of eggs, greater production of milk, and so on. The genetic differences among fowls in rate of growth have been utilized by those developing special fast-growing strains and crosses for the production of broilers. Similarly raisers of beef cattle are finding that some sires differ from others in the ability to produce off spring that can make consistently efficient gains. A detailed discussion of this subject is beyond the scope of this book.

From the few examples cited in this chapter it seems clear that genetic differences in metabolic processes have much to do not only with the viability and health of domestic ani mals, but also with the profits or losses of every producer of livestock. They merit further study

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Chapter VIII

Ways of Resisting

THE evidence reviewed in the foregoing chapters shows that in domestic animals, from honey bees to horses there are remarkable differences in genetic resistance to disease. Recognition of this fact raises some important questions. Is resistance general or specific? In other words, are animals genetically resistant to one disease equally able to withstand others? How do resistant animals differ from susceptible ones? Can the two sorts be distinguished easily by inspection, or by simple laboratory tests? Obviously if they could be so distinguished at early ages and without actually exposing them to disease the process of breeding highly resistant strains could be greatly accelerated.

There is another important question Can resistant strains be bred without deliberate and constant exposure to disease? In breeding fowls resistant to leucosis at Cornell, such exposure provided the only means by which resistant families could be differentiated from susceptible ones. As it turned out, the results (see Chapter VI) fully justified that procedure. On the other hand, few breeders of livestock (and still fewer veterinarians) are likely to be receptive to the idea that disease should be encouraged to lurk on the premises in

order that resistant and susceptible animals can be recog nized. If there were some peculiarity of the skin hair blood, urine, or anything else whereby the two types could be dis tinguished disease resistant strains could be bred even with out exposure In such cases most breeders would discard the recognizably susceptible animals.

As we shall see later in this chapter there is at least one case in which resistant and susceptible animals can be easily distinguished merely by visual inspection. There may be others. No such simple path to progress has yet been found for leucosis in fowls, but the possibility is not excluded that some simple way to identify resistant birds may still be found. In the meantime we poultry breeders can make a virtue out of necessity for some exposure to leucosis seems inevitable in most flocks All we need to do to intensify that exposure is to brood our chicks as close as possible to the adult birds that carry the infection Most breeders of live stock can think of other diseases to which exposure seems inevitable without any special efforts to encourage its pres ence. Mastitis in cattle is a good example

Unfortunately our knowledge of the mechanisms whereby domestic animals resist disease is slight. It seems desirable therefore, to review what little is known, if only to show the paucity of facts the importance of the subject, and the kind of research that is needed

It is not within the scope of this book or the competence of the author to review the whole field of immunology In more ponderous volumes one may read of the defenses against disease that are provided by the outer fortifications—the skin and the mucous membranes and their secretions—and of the tactics employed by the defending antitoxins, pre cipitins, cytolysins agglutinins and other antibodies and by the phagocytes that engulf invaders one may read also of

the opsonins and of the blood complement so necessary for efficient operation of the defending army

All that can be attempted here is to consider briefly how genetically resistant animals differ from genetically susceptible ones. A lot of work has been done in that field with small rodents and other laboratory animals and much of it has been reviewed by Gowen (9) For larger animals there is comparatively little to report. Here lies a promising field of research for geneticists and pathologists interested in farm animals It would seem desirable that they start when young, be endowed with great patience and be willing to wait for the scientific rewards of their labors, but they should be amply remunerated otherwise while waiting Rome was not built in a day Genetic experiments with cattle need more time than similar experiments with mice

Is resistance general or specific? Animals highly resistant to one disease can be very susceptible to another This point was nicely illustrated in some tests by Gowen (8) with three different strains of mice (Fig 27) The strain most resistant to mouse typhoid proved highly susceptible to the virus of pseudorabies. Of two strains equally resistant to the latter disease, one was much more susceptible to ricin an antigenic poison, than the other

A similar situation was seen in our three strains of White Leghorns at Cornell in 1949 In them mortality from blue comb disease (at about 5 to 4 months of age) and from leucosis (up to 500 days of age) was as follows

	Blue comb per cent	*Leucosis per cent*
K Resistant strain	0.99	6.5
C Resistant strain	7.40	8.7
Susceptible strain	0.00	65.0

In further studies with these three lines Carson (6) showed that the two strains highly resistant to leucosis were somewhat susceptible to the organism causing fowl cholera, but the strain susceptible to leucosis was comparatively resistant

Figure 7 Differing susceptibility of three strains of mice to three pathogenic agents, showing that genetic resistance to one disease can accompany susceptibility to others. (After Gowen 1 *Journal of Heredity* 937)

to cholera. It was also resistant to a coccidium *Eimeria tenella* and to infectious bronchitis. One of the strains resistant to leucosis was also comparatively resistant to Rous sarcoma to infectious bronchitis and to *Salmonella pullorum* but the other leucosis-resistant strain was not equally good in these respects.

These few examples are enough to indicate that the physio-

logical basis for genetic resistance to one disease must be different in many cases from those concerned with resistance to others This makes more difficult the problem of breeding strains that are resistant to several diseases On the other hand, animals genetically resistant to one organism are some times also resistant to another that is closely related to the first. Thus, Leghorns are comparatively resistant both to *S pullorum* and to *Salmonella gallinarum* There is also encouragement in the fact that some genes do provide general resistance to infections of different kinds. One of these is considered in the following paragraphs

Defective blood complement in guinea pigs. At the Vermont Experiment Station, Rich (25) made a remarkable study of guinea pigs that were genetically deficient in blood complement. That important part of the defense mechanism is required for the function of antibodies, helps to destroy invading cells, and supplements other defense mechanisms in ways not yet fully understood.

In Rich's deficient guinea pigs it was shown by a remarkably conclusive series of genetic tests (yielding altogether 5 585 animals) that the defective complement resulted from homozygosity for a recessive, autosomal gene. From matings in which both parents had the defect, no less than 2,046 offspring were produced, all deficient like their parents.

Tests of the susceptibility of these deficient animals were made by inoculating them and their normal litter mates with *Bacillus cholerae suis* (now *Salmonella choleraesuis*) Among those deficient in complement mortality was 77 per cent, whereas those that had normal blood complement lost only 20 per cent. Since guinea pigs heterozygous for the defect all had normal blood, it is clear that the dominant allele —even in single dose—was enough to ensure the production

of that normal blood and the associated comparatively high level of resistance to infection

The guinea pigs deficient in blood complement also proved to be highly susceptible to other infections When it seemed probable that the whole lot might be lost because of their general susceptibility some of them were sent to other institutions in an attempt to preserve the strain Rich s find ings were confirmed by Hyde (12) whose studies showed that the causative gene (when homozygous) eliminates the third component of blood complement the part that is resistant to heat but absorbed by yeast.

A similar defect has not yet been identified in other domestic mammals, but it could occur in any of them.

Resistance related to sex and age Numerous afflictions are limited to one sex or to the other because of anatomical or physiological differences between the two Apart from such situations a familiar example of a remarkable sex difference in susceptibility to an infectious disease is provided by erysipelas in turkeys. Madsen (18) described an outbreak that killed 525 birds in a single flock From his figures it is evident that the mortality rate was about 46 per cent among the males but only 4 per cent or even less, in the females. An unanswered question however is whether the greater susceptibility of the males results from some sex difference in physiology or merely from their normal belligerency This last makes them more likely than the females to get their shanks and their gorgeous head furnishings scratched and thus to permit infection by the causative bacterium.

Burmester and Nelson (4) have shown that in the fowl females are more susceptible than males to lyphomatosis. On the other hand as Campbell (5) has found female rats are naturally more resistant than males to the larval form of the

tapeworm, *Taenia taeniaeformis* In both these instances there was experimental evidence to show that the sex difference in susceptibility is dependent upon a corresponding difference in sex hormones.

Effects of age on resistance vary with different diseases and different species In cattle, susceptibility to the mastitis caused by *Streptococcus agalactiae* increases with age. In the fowl, susceptibility to leucosis is greatest immediately after hatching, but it decreases thereafter at such a rate that by 5 months of age most birds are immune to infection if they have not previously been exposed. On the other hand, young chicks are more resistant to moderate doses of coccidia than adults that have never been exposed. Similar age differences in susceptibility will occur to most readers.

Differences among species in resistance Examples of remarkable differences among closely related species in susceptibility to disease are well known. Thus, one mosquito *Anopheles maculipennis* will carry the plasmodium causing malaria but *Anopheles punctipennis* does not. The house mouse *Mus musculus* is resistant to infection by *Bacillus piliformis* but the Japanese waltzing mouse, *Mus bactrianus* has proved to be highly susceptible.

Among domestic animals there are similar cases some of which are very important. The domestic fowl is remarkably resistant to *Histomonas meleagridis* the flagellate causing blackhead (enterohepatitis) but the turkey is very susceptible to that same parasite. Because it can be carried by the common cecal worm of the fowl it is important that susceptible turkeys should not be raised on the same ground with resistant chickens. The comparatively high susceptibility of the turkey may possibly result from the fact that natural selection has probably operated on that new-world species for

only 450 years or less whereas the domestic fowl has been exposed to that biologically beneficent process for some thousands of years. Measles and firewater were not the only afflictions that Europeans brought to the natives of North America

Resistance of Zebu cattle to tick-borne diseases A much more important difference between species in resistance to disease is the remarkable resistance of cattle of the Zebu type to excessive heat (Chapter II) and to tick borne diseases. The statements of several writers that various breeds of the humped, short haired Zebus (*Bos indicus*) are generally more resistant to tick borne diseases than European cattle have been confirmed in a remarkable series of studies by Bonsma (1) at the Mara Experiment Station in the Transvaal in South Africa. That post was established in 1936 to breed cattle resistant to tropical conditions and if possible resistant also to tick borne diseases. In order to stock this station, animals were brought in from other parts of the country Most of these were Africanders (Zebus) but some were exotic breeds of *Bos taurus* including Aberdeen Angus, Herefords, Short horns, Red Polls, and Sussex.

Bonsma's report is concerned primarily with heartwater a disease caused by a rickettsia and carried by the bont tick, *Amblyomma hebraeum* On the infected Mara premises mortality from heartwater among the introduced cattle in the first two years after their arrival was 41 2 per cent among exotic breeds from areas free of heartwater but only 13.6 per cent among Africanders from those same areas. Among 207 Africanders from areas known to be infected, not one death from heartwater occurred Among the exotic breeds from heartwater areas there were two classes Some of them came from farms on which dipping to kill ticks was a regular

practice The remainder came from farms where dipping was not a regular practice. None of the latter cattle con tracted heartwater at the Mara Station but 31 per cent of those from the dipped herds did so

Bonsma interpreted these facts as showing that regular dipping prevents the development of natural immunity In other words genetically susceptible calves were protected by the regular dipping that removed their ticks In the ex posed herds that were not dipped presumably such calves were eliminated early by natural selection. Mature animals

Table 14 Mortality from heartwater to 30 months of age in cattle born at Mara

Breed	Calves born, umber	Died, per cent	Average age at death, months
Pure Africander	246	5 3	
¾ Africander ¼ European	66	7.0	8
½ Africander ½ European	897	0.2	6
Pure European	28	60.7	5

From data of Bonsma J *Farming in South Africa* 1944

brought to Mara from these undipped herds would have been those genetically capable of developing immunity which is established in high degree by the age of 18 months.

The foregoing figures show that the Africanders whether previously exposed or not, were significantly more resistant than the comparable samples of the exotic breeds. Similarly *among the calves born from the introduced stock at the* Mara Station, mortality from heartwater was more than 11 times as high in the exotic breeds as in the pure Africanders (Table 14) Moreover among calves that did succumb the Africanders were able to survive over twice as long as those of the exotic breeds. It is remarkable that the crossbred

cattle should have shown such a relatively high degree of resistance That finding, however confirms the previous report by Zuravok (29) of high resistance to other tick borne diseases in the F_1 offspring from the cross of Zebu × European cattle

Cattle that came to Mara from infected areas did not produce offspring any more resistant than calves from cows brought in from areas free of heartwater It seems probable, therefore, especially since about 70 per cent of the introduced cows calved within 2 months of their arrival that none of the resistance shown at the Mara Station could be attributed to any passive immunity that might have been transmitted from highly immunized dams to their offspring

To determine the comparative susceptibility of Africander and exotic cattle to ticks, regular monthly counts were made on 12 cows of each kind for 12 consecutive months For each animal and at each counting, the number of ticks was recorded on four separated areas of 200 square centimeters each on the body and on 200 square centimeters of the escutcheon and inner thigh. Those under the tail were also counted. After each count every cow was dipped to remove all ticks and thus to ensure a uniform start in the contest to see which could accumulate the fewest ticks in the ensuing month The sums of these counts for the full year (which recorded 14 867 ticks on these limited areas alone!) showed that in all three regions the numbers of ticks were remarkably fewer on the Africanders than on the exotic breeds (Table 15) Bonsma attributed this in large measure to the fact that the former have a comparatively thick skin which is less attractive to ticks. Proof of this is seen in the fact that his tick counts were highest for the comparatively thin-skinned areas (the escutcheon and under the tail) and lowest for the thick skin on the side of the body Actual

measurements of the thickness of a double fold of skin showed that the Africanders had significantly thicker skin than the European breeds in all of the six areas measured (Table 15). More recently other investigators have found that a thick skin is not characteristic of all breeds of Zebu cattle

Table 5 Comparison of Africander nd European cattle with respect to numbers f ticks and thickness of skin

Item measured	Totals for x cows of each kind		Ratio European. Africander
	Africander	European	
Number of ticks; 12 counts per cow			
On the body 800 square cm.	15"	7"5	7.5
On the escutcheon 200 square cm.	589	4,397	9
Under the tail	40	4,789	2
A g thickness of skin double fold.			
In three thick-skinned regions, mm.	2.03	9.89	—
In three thin-skinned regions, mm.	7 5	6.22	—

From data of Bonsma in F rms g South Afric 911

Some idea of the difference between Bonsma s two types of cattle in length of hair is shown by the fact that in summer after the cattle were dipped, cows of the exotic breeds lost about one-half gallon more fluid while draining in the drying pen than did the Africanders. In winter when the coats of both were somewhat longer the difference was even more pronounced Of all ticks counted on the 12 cows of each type, the proportion found on the Africanders was only 7.4 per cent in the summer months, when the coat of hair was short and glossy but it rose to 17 per cent in the winter when that coat was longer and rougher

Finally having come to the conclusion that the thick, loose skins and short glossy coats of the Africander cattle made them less attractive to ticks than the European breeds with their thinner skins and longer hair Bonsma tested that conclusion experimentally Six Hereford cows were classified as likely to carry either few ticks or many This was done by visual inspection only without any measurements. Thick skins can be identified because they show a greater number of vertical skin folds than do thin skins. After the three Herefords considered most likely to repel ticks had been identified, measurements of the thickness of the skin were taken in six places on each cow making 18 determinations altogether Only two of these 18 areas differed from Bonsma s visual classification as thick-skinned or thin-skinned. Subsequent counts of ticks on these six cows for 12 months revealed that the number on Bonsma s three thick-skinned Herefords was only 56 per cent of that for his thin-skinned group

Altogether these studies have shown that Africander cattle are significantly more resistant to heartwater than European breeds and that their resistance is associated with better ability to repel ticks That biological superiority in turn, is apparently attributable to the thicker skins and shorter glossier coats of the Africanders. Similar differences can be easily recognized among cattle of European breeds hence selection is feasible within them for the ability to repel ticks and thus to escape tick borne diseases.

Among the ticks infesting cattle at the Mara Station bont ticks, which carry the rickettsia causing heartwater were greatly outnumbered by blue ticks, *Boophilus decoloratus* (or *Margaropus decoloratus*) which carry the sporozoan causing piroplasmosis. Monthly counts on 36 animals for a year showed that the Africanders carried significantly fewer of

both kinds than did exotic cattle. The mortality from piroplasmosis was not given but that disease was apparently considered less serious than heartwater

In crossbred cattle Bonsma s tick counts were intermediate between those of the two parental types but closer to those of the Africanders. This may explain why the degree of resistance in crossbreds to tick borne diseases is more like that of their Zebu parent than of their European one. This has been demonstrated not only with respect to heartwater in hybrids from Africanders (Table 14) but also for other tick borne diseases and in crossbreds from other cattle of the Zebu type (Zuravok, 29).

Disease resistance and klendusity Paradoxically it has not yet been shown that the disease resistant Zebus are better able than European cattle to resist actual infection with tick borne diseases. From the available evidence it appears more likely that the Zebus *escape* those diseases by repelling the ticks that carry them That repulsion is by no means complete, and yet mature animals in infested areas show a degree of resistance to tick-borne disease that approaches complete immunity

These facts suggest that the special value of the protective skin and short, smooth coat in cattle of the Zebu type is to reduce the infestation by ticks to numbers that ensure a small, immunizing dose but make a large, lethal one less likely If that is correct, the question whether Zebus and European cattle differ in ability to withstand a uniform dose of some rickettsia or sporozoan remains to be answered.

To distinguish between (1) the ability to resist disease after infection and (2) the ability to escape infection, Rankin (24) coined for the latter happy attribute the term "klendusity It means to bar the entrance or "to keep out"

and is derived from the first three letters, *kle* of the several Greek words meaning "to bar" "to close" "to keep under lock and key" and so forth and the Greek *endusis* meaning "an entering in" or entry Rankin observed that raspberries of the Herbert variety seldom get mosaic disease because they repel the aphid vector that carries the causative virus, but that those which do become infected show that the variety is extremely susceptible It is klendusic, but not resistant. The same applies to the Lloyd George raspberry in which fine leaf hairs prevent aphids from getting at the leaf Other plants may be klendusic because of their thick cuticle as *the Africander cattle* appear to be

It remains to be determined whether these animals can provide only a fair degree of klendusity or whether they have also a high degree of resistance to infection. In either case the Zebus can contribute something that is of inestimable value to the many tick infested regions of the world.

Resistance to pullorum disease in the fowl For about a quarter of a century I have been curious about the basis for genetic resistance to *S pullorum* Some interesting facts have accumulated, thanks chiefly to some graduate students who shared my curiosity and became perforce assiduous devotees of the cult of the rectal thermometer As a result of their unflagging efforts, it now seems clear that resistance to pullorum is associated with superior control by the resistant chick over its thermoregulatory mechanism

An obvious starting point was to determine, if possible, why Leghorns are more resistant than heavy breeds (see Chapter VI) Guided by Pasteur's classical demonstration that the fowl's immunity to anthrax results from its high body temperature, the first question was whether or not the Leghorns differ in temperature from susceptible breeds

Adult birds do not, but with newly hatched chicks—the age most susceptible to pullorum—it is a different matter

Until shortly before it hatches, the incubating chick is a cold-blooded animal, its temperature being no higher or lower than that of the circumambient air Once pulmonary respiration is started (when the chick pierces the air cell of its egg on the twentieth day of incubation) conversion to the homoiothermic state begins. It is a slow process. On the day after hatching, chicks have temperatures of about 103 F or less, and they do not attain adult temperatures (105–109 F) until they are about 10 days of age or more.

An important early discovery was that White Leghorn chicks are able to raise their temperatures more quickly in the first 10 days after hatching than can Rhode Island Reds (11 16) Furthermore at subnormal brooder temperatures, when the body temperatures in both breeds are lowered correspondingly the Leghorns are able to attain almost normal temperatures by 10 days of age (Fig 28) but the Reds lag far behind after the first 4 days (26) It was then found that by brooding chicks at 28 C. rather than the usual 35 C., their body temperatures could be lowered by 0 7 to 1.4 F and that there was a highly significant reduction in the ability of chicks thus chilled to resist pullorum A similar reduction occurred when chick temperatures were temporarily lowered (as much as 8.4 F) by the injection of sodium amytal. Conversely in chicks subjected to artificially induced fever (0 63 to 1 34 F above normal) by temporary exposure to a carbon filament lamp resistance to pullorum in 10 different trials was consistently greater than in controls.

It does not follow that in these overheated chicks the infection was vanquished merely by getting body temperatures up to the thermal death point of the bacterium, as is possible with gonococcal infections in man. The fact that Lamoreux

(15) found body temperatures above 109° F. in adult fowls that reacted positively to agglutination tests for *S. pullorum* suggests that the thermal death point of that organism must be still higher. Accordingly, it seems more likely that high

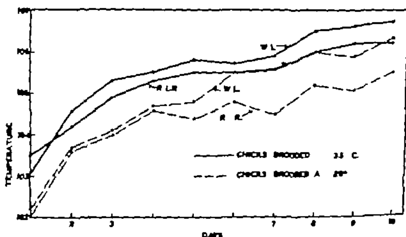


Figure 28. Average daily body temperatures after hatching, showing more rapid rise and better control (at 28° C.) in White Leghorn chicks than in Rhode Island Reds. (From Scholes and Hutt in *Cornell Agricultural Experiment Station Memoir 244.*)

temperatures in the chick aid resistance by accelerating the normal complex mechanisms for defense.

In chicks inoculated orally with *S. pullorum* within 24 hours after their removal from the incubator, average body temperatures to 8 and 10 days of age are significantly higher than in uninoculated controls (23, 26), but they are more variable. (Healthy uninoculated chicks show so much variation in temperature from day to day, even when temperatures are recorded at the same hour in a controlled environment, that a single reading is of little value. For that reason, we have recorded temperatures daily to 10 days in many cases, and for 5 days or more in most others.) Both Scholes (26)

and Ram (23) found the average temperatures after infection to be higher in resistant chicks than in susceptible ones. Both kinds show a distinct febrile reaction but the susceptible chicks are less able to maintain that fever (Fig 29)

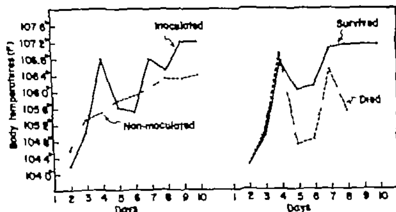


Figure 29. Body temperatures at t days of age showing febril reaction in chicks inoculated with *S pullorum* and inability of susceptible chicks to maintain temperatures. (From Ram and Hutt in *American Journal of Veterinary Research* 955.)

By inoculating chicks at 2 or 3 days after hatching, at which time two or three daily readings of body temperature had already been made, Scholes was able to show that those which eventually succumb to infection have subnormal temperatures right from hatching

Other evidence of the importance of body temperature in determining resistance came from families of chicks that were fully pedigreed, i.e. identified as to sire and dam. Among these from daily temperatures of normal, uninoculated chicks for 8 or 10 days, it was possible to distinguish families characterized by temperatures above or below the average for all chicks. Other samples from these same families

were then inoculated with standard doses of *S. pullorum* to compare the resistance of high-temperature and low-temperature families. With 18 such families (all Rhode Island Reds) tested by Scholes (26) in five trials and 22 others (all crossbreds from two sires) tested by Ram (23) in nine trials, mortality from pullorum disease was greater in every case in the low-temperature families than in the high-temperature ones. Ram's data for tests with 621 inoculated chicks show

Table 16. Differences in temperature and mortality between families within progeny of each sire

Sire	Dams families		Average body temperature (F.)	Chicks inoculated	
	Temperature class	Number		Number	Died %
A (high temperature)	High	5	105.2	145	51
	Low	4	104.5	87	42.5
B (low temperature)	High	7	101.7	[illegible]60	58.5
	Low	6	104.2	29	67.4

From data of Ram and Hutt in *American Journal of Veterinary Research*, 1935.

clearly that chances of survival are best for chicks from sires and dams both of which produce offspring with temperatures above average during the first 5 days after hatching (Table 16). Conversely, mortality was more than twice as high in chicks from parents that both yielded low-temperature families.

Severens *et al.* (27) concluded that chicks resistant to pullorum differ from susceptible ones in having a greater proportion of lymphocytes, particularly during the first 5 days after hatching. However, their resistant strains were White

Leghorns, but their susceptible strain was a Rhode Island Red. Since these breeds differ in several other important physiological traits (see Chapter VII) including chick temperatures, it seemed desirable that further studies be made to determine whether resistance depends on temperatures, or lymphocytes, or on both

Ram (23) found that the proportion of lymphocytes rises steadily in the first 8 days after hatching, as does body temperature, but that these two variables are not closely related Familial differences in percentages of lymphocytes were small, statistically insignificant, and unrelated to mortality from pullorum. Brooding chicks at 40 C. depressed the lymphocyte count but raised both body temperatures and resistance. Finally Ram's White Leghorns, like those of Severens *et al.* had consistently higher lymphocyte counts and greater resistance to *S pullorum* than did Rhode Island Reds On the other hand, his crossbred chicks had even lower counts of lymphocytes than the Rhode Island Reds, but they were just as resistant as the White Leghorns For these reasons and others it seems clear that lymphocytes have no special relation to the chick's defenses against pullorum. However one response to infection with that organism is a rise in total leucocytes and Ram confirmed the earlier evidence of Kelly and Dearstyne (14) that the heterophils are responsible for that rise

Altogether these studies have shown that genetic resistance to *S pullorum* is associated with superior thermoregulation Possession of that desirable attribute is evidenced by comparatively rapid transition from the poikilothermy of the embryo to the homoiothermic state of the chick at 10 or more days of age It is also shown by better ability on the part of the chick to control body temperatures when chilled. Similarly Locke (17) has shown that rabbits able to recover nor

mal temperatures within 55 minutes after chilling are more resistant to infection with virulent pneumococci than those unable to do so

The view that the resistant chick utilizes its superior thermoregulation to resist infection is supported by the sustained febrile reaction of inoculated chicks. Fenn (7) found that the rate of phagocytosis is almost a logarithmic function of temperature It seems probable that other defense mechanisms, such as the production of antibodies and bacteriolysis, may be similarly accelerated at temperatures higher than normal

Resistance to fowl typhoid. One might expect the mechanisms for resisting *S gallinarum* to be similar to those for resisting *S pullorum* Bell (1) found normal body temperatures at 9 to 25 days of age to be higher in resistant chicks than in susceptible ones. Chilling lowered resistance of both kinds, but resistant chicks were better able to maintain normal body temperatures.

Chicks of resistant and susceptible strains did not differ in the rate of phagocytosis as studied *in vitro* That process was accelerated in both kinds by rising temperatures However Bell found that lysis of bacteria within polymorphonuclear leucocytes proceeded more rapidly in those from resistant strains than in the others and he considered that to be a major factor in genetic resistance to *S gallinarum.* Unfortunately his susceptible strain was of one breed (New Hampshire) and his resistant strains of another (White Leghorn and Leghorn crosses) Further studies with genetically resistant and susceptible chicks of some one breed are desirable

Resistance to mastitis. The belief still persists in some quarters that mastitis is an inevitable penalty that the dairy industry must pay for having pushed its cows to higher and

higher production A careful study of the possible relation ship between high production and its relation to disease in dairy cattle led Ward (18) to conclude that no such basis for udder troubles exists. Cows showing little or no sign of mastitis had higher butterfat production per lactation period than did those that developed serious udder trouble. In another phase of this same study cows that were high producers in their first two lactation periods were found to last longer in the herd than did low producers For these reasons Ward concluded that it is still obvious that no case exists for suggesting that the high producer breaks down more quickly than the low-producing cow

The ways by which some cows resist infection of the udder while others similarly exposed cannot do so remain to be determined, but careful investigators have disproved some of the more plausible theories. Thus, Murphy (19) concluded that injury to the teat is, at best, only a minor factor in infection of the udder He also found that the amount of pocketing in the mucous membrane of the teat was not related to mastitis (20) Murphy and Stuart showed that the degree of susceptibility to infection with *S agalactiae* is not related to patency (or looseness of the teat's mechanism for closing) as measured by the maximum rate of milk flow (22)

Although evidence of genetic differences in susceptibility to mastitis has been available for over 20 years, to the best of my knowledge no effort to breed resistant stock has yet been reported, but one can still hope A difficulty confronting any such attempt is that susceptibility increases with age. It is highly desirable to be able to distinguish between resistant and susceptible females at an early age, not only so that the latter may be eliminated early but also to learn which sires and dams are producing resistant offspring

Some tests made by Murphy and Stuart (21) suggest that

the difficulty of early recognition may be circumvented by artificial inoculation in the teat canals with *S agalactiae* Six comparable cows in their first or second lactations were thus exposed in all four quarters of the udder and any subsequent infection was observed during the next 2 weeks. Infected animals were then cleaned up with massive intramuscular doses of penicillin and after that substance had disappeared from the milk were ready for a repetition of the test. Each cow was thus subjected to four cycles of tests in a period of 5 months, making a total of 16 exposures (4 per quarter) per cow

Of these six cows two became infected at all or nearly all exposures one only once another thrice, and two not at all. Clearly infection by *S agalactiae* is not a matter of chance. It depends on the individuality of the cow With such a test applied as a routine procedure to young heifers, differentiation of resistant and susceptible animals should be feasible at a comparatively early age and, with proper selection it should not be difficult to raise the level of resistance in the herd

In fairness to Murphy and Stuart it should be made clear that they did not recommend such deliberate exposure It is doubtful that many veterinarians would do so at this time

Protective pigment around the eyes of Herefords It is well known that Hereford cattle in areas having much bright sunlight are subject to sore eyes which range in severity from slight conjunctivitis to true cancer (epithelioma) The latter stage is seldom seen according to Guilbert *et al.* (10) in animals under 4 years old Among 228 Herefords over that age the incidence of conspicuous lesions of the eye was 10 5 per cent half of which were so bad that the animals were disposed of Significantly the first lesions occurred only

on unpigmented portions of the lower eyelids—never on areas that carried red pigment.

Similar evidence from 560 Herefords reported by Bonsma (3) shows that a ring of red pigment around the eye apparently gives almost complete protection against the trouble The incidence of ophthalmia, other affliction and cancer in the 1 120 eyes of his Herefords was as follows

Degree of pigmentation	*Eyes number*	*With lesions per cent*
Absent, or almost entirely so	359	34.0
Some pigment on lids but ring around eye less than ½ inch wide often broken	659	8.3
Ring of pigment at least ½ inch wide around eye	102	0.0

From such records it would seem highly desirable that breeders of Herefords in areas subject to strong sunshine should select against the all white heads that look so well and give preference for breeding to those carrying a ring of pigment around the eye. In one of the herds observed by Bonsma, such selection effectively increased the proportion of animals having that desirable protection.

Breeders of Aberdeen Angus proclaim proudly that cancer of the eye is unknown in that breed. Similarly black sheep are said to be preferred to white ones in some regions of North Africa because their pigment protects them against the photosensitivity that is common there from eating plants of the family Hypericaceae

Blowfly strike in sheep Studies in Australia (13) have shown that much of the trouble from blowflies depends on predisposition or attractiveness, of the sheep that are stricken

Sheep predisposed to strike are likely to show one or more of these faults slack open fleece especially over the withers wool lacking in quality as indicated by handle character and yellow coloration of yolk faulty conformation as shown by pinch behind the withers, high shoulder blades, broad withers with depression between the shoulder blades. Those particularly subject to crutch strike show excessively loose skin and wrinkles in the breech

The measures recommended by the Joint Blowfly Committee (13) to reduce inherent susceptibility to strike emphasize the importance of selective breeding to eliminate or reduce these defects Unfortunately the desirable plain breeched rams and ewes do not breed true to type, but some rams were found to produce higher proportions of plain breeched lambs than others Accordingly progeny tests are recommended to find the most desirable rams Breeders are *encouraged by the assurance that the highly desired plain* breech can be had without any loss in the quality and weight of the wool

Rhinitis in swine While pathologists search for the bacteria, viruses and trichomonads that have been incriminated at various times as pathogens responsible for this affliction it may do no harm to suggest that some pigs are able to avoid this trouble merely by keeping a straight face In Canada the disease is now less common than it was in earlier years. Inquiries elicited the information that the disease occurred more frequently there until breeders deliberately selected against the dished faces which they had found to be associated with rhinitis. Constriction of the nasal passages might be an aggravating factor but straight faced animals could differ in susceptibility to infection Unfortunately precise information from controlled experiments is not available.

The only justification for mentioning rhinitis here is the possibility that these lines may encourage someone to attempt to breed a straight faced, resistant strain while maintaining at the same time and place a stock of dish faced, snuffling pigs as controls.

A friend who has bred swine for many years but who prefers to remain anonymous (to protect the reputation of his stock, as usual) assures me that in his experience some families are more susceptible to rhinitis than others.

Summary The few cases cited in this chapter show that resistant animals differ from susceptible ones in ways that can sometimes be detected with a little careful search. Indicators of resistance can accelerate the breeding of disease resistant strains. The fact that there is so little to report in this field suggests that there is ample scope for further research on the bases for resistance to disease in domestic animals. The greatest returns are likely to come from co-operative research by pathologists, physiologists, and geneticists.

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Chapter IX

Ways to Use Resistance

AN old physician with long experience once said to me "In most cases we don't cure the patient. Nature effects the cure; all we do is to help her along with that process." He was speaking of individual patients—not of the human race—but a similar situation applies to the breeds, strains, flocks and herds that are the patients of the animal breeder. Even under domestication natural selection eliminates many of the unfit. All the geneticist does who breeds disease-resistant stock is to ensure exposure to disease and then, by using the best techniques of breeding, to accelerate the accumulation of genes for resistance.

Wild animals, like domestic ones, are subject to disease, but it is doubtful that disease alone has ever extinguished a species. In those cases that we can observe, when wild animals are stricken with some hitherto unexperienced affliction, even though it may seem disastrous, there are always some survivors. Multiplication of such resistant individuals results in the development of resistant races. Examples of such conquests over disease by wild animals regularly exposed are seen in the prolific oysters of Prince Edward Island (see Chapter IV), in the house flies that learned to thrive on DDT and in the rabbits that are now becoming resistant to myxo-

selection to eliminate, not only the individuals that proved most susceptible but also the breeding animals that seemed to transmit susceptibility to their offspring Conversely selection for resistance could be carried on to build up the average level of resistance in the herd.

Slaughter of the innocents The evidence reviewed in Chapter VI shows that there are genetic differences among fowls in ability to resist, not only infectious bacteria, viruses, and fungi but also parasitic protozoa and worms. Every attempt to raise resistance by selection has been successful.

In striking contrast to that record eight years efforts to eradicate the mild form of Newcastle disease by slaughter in England (where it is called fowl pest) proved completely futile, and in 1956 the ninth year of attempted eradication, more birds were slaughtered than ever before (Table 17)

Table 17 Birds slaughtered in Great Britain in the attempt to eradicate fowl pest (Newcastle disease)

Year	Fowls	Ducks	Geese	Turkeys	Others
1948	47,962	2,868	902	9,535	126
1949	87,205	5,083	838	542	476
1950	67,276	82	[illegible]03	42	84
1951	58[illegible]266	8,736	[illegible],024	2,789	904
1952	298,334	2[illegible],418	616	2[illegible]3	134
1953	558,7[illegible]2	50,739	3,025	4,569	5[illegible]7
1954	6[illegible]2,208	6,960	1,271	[illegible]0,376	25
1955	485,583	9,012	1,6[illegible]0	10,270	26
1956	1,086,317	92,329	1,64[illegible]	25,[illegible]24	[illegible]77

From *Reports on the Animal Health Services in Great Britain*, 1951–1955, 1956. By permission of the Controller of Her Britannic Majesty's Stationery Office.

In these efforts to eradicate Newcastle disease, the slaughter is not limited to the sick birds in a flock. All must go—

including the genetically resistant fowls which greatly out number the susceptible ones. Many of the flocks slaughtered are in perfect health and laying so well that presence of the disease is completely unsuspected until it is revealed by a blood test. Among the fowls thus slaughtered was the breeding stock of one of the best poultry breeders in the British Isles whose pedigreed flocks were wiped out no less than four times in nine years of attempted eradication.

The mild form of Newcastle disease has gradually worked its persevering way around the world, and it has now been in the United States for about 15 years. Fortunately it had spread from coast to coast before it was recognized as New castle disease and any attempt to eradicate it by slaughter was out of the question. Efficient vaccines have been devel oped, some of which can be administered merely by putting them in the drinking water

Many poultrymen, however have ceased to vaccinate be cause they no longer consider the disease serious enough to warrant that protection. In most flocks that become infected, there is little mortality or none, but the birds cease laying for periods varying from a few days to 3 weeks. After re sumption of laying they usually do as well as before unless some other condition intervenes. Hatcherymen continue to vaccinate because they dare not risk having their supply flocks thrown out of egg production at a time when eggs are needed for the incubators.

In Lancashire, England, there is a greater concentration of poultry than in other parts of the country There annually for the past nine years, with the first chill winds of November Newcastle disease has made its appearance. So have the official veterinarians. Through the winter months the slaugh ter has proceeded apace and by April the disease has usually been wiped out. So has many a productive flock most of its

members in perfect health highly resistant to Newcastle, and in no worse condition than a child that has recovered from chicken pox.

The record in Table 17 shows little sign that this annual cycle of events will terminate in the near future The amount of compensation paid in 1956 for slaughtered flocks was £1 371 710 ($3 840 788). With an annual expenditure less than half of 1 per cent of that sum and within 10 years, the feasibility was demonstrated of conquering leucosis by breeding resistant strains. How fortunate that there is no blood test for that disease!

Genetic resistance combined with other control measures. The keeping of genetically resistant stock does not make it unnecessary to use ordinary good husbandry and practices of management that are conducive to the comfort of the animals and a minimum of disease Plant pathologists have found that a combination of genetically resistant varieties with fungicides and insecticides (when needed to reduce insect vectors) frequently provides better control than any one of these defenses alone. It is probable that similar combinations of genetic resistance with other control measures may do the same with respect to diseases of animals

This has already been demonstrated for one of them at least. There is no great difficulty about breeding strains of fowls resistant to leucosis. As it happens, however less than 1 per cent of the poultry raisers in the United States are also poultry breeders The great majority buy their chicks each year from commercial hatcheries. Accordingly for most people raising chickens the best procedure to follow is to raise the chicks in isolation, as complete as is practicable, from the older birds that carry the disease When that isolation is almost complete losses can be reduced to an insignificant

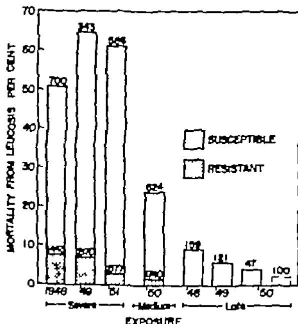


Figure 30. Mortality from leucosis from 42 to 500 days of age in four annual generations of White Leghorns. *Figures above the columns give the n mbers* of females in the different groups. The protective value of genetic resistance is shown by comparisons between the resistant and susceptible strains, when exposure was severe and when it was of medium intensity (in 950). The protective value to genetically susceptible stock of isolation during the critical early ages is shown by comparisons i 1948 nd 949 between such birds exposed severely right after hatching and their full sisters not exposed until 60 days later The short, dotted column t the right represents genetically resistant birds exposed late, among which not one died of leucosis. (From Hutt and Cole in *Science* 955)

level even in a highly susceptible stock (Fig 50) Unfortunately complete isolation is not often possible and on many poultry farms it may even be difficult to provide the partial measure of it that gives appreciable protection. It is desirable therefore that the hatcheries supply chicks that are genetically as resistant as they can be made. Some of the hatcheries are now breeding their own resistant stock. For others it would seem desirable to head their supply flocks with males of the genetically resistant strains or to multiply the resistant crosses now being developed by the better breeders.

Finally for that 1 per cent or fewer of the poultrymen that actually do breed chickens there is the special responsibility of attempting to breed highly resistant strains. When the desirable genes thus accumulated in them are multiplied by the hatcheries and when chick buyers isolate their chicks from older birds mortality from leucosis can be reduced considerably below the levels that once prevailed.

Records for some experiments in exposure and isolation of our resistant and susceptible strains here at Cornell (Fig 50) show not only that it is possible to provide protection against leucosis for a highly susceptible strain by raising it in isolation but also that genetic resistance can provide equally good protection for chicks that are severely exposed (4)

Distribution of resistant stock Maximum use of resistant strains developed in any one part of the world can be obtained if those strains maintain their resistance in other regions. In some cases it has been shown that they do so and it seems probable that they will in most

The special qualities of the Zebu types of cattle have been demonstrated in America, the West Indies, South Africa India the Philippines, and Australia. In all of these places

those qualities are being used to raise resistance to excessive heat, to tick-borne diseases, or to both. Similarly Stewart (8) observed that cattle resistant to trypanosomiasis in the Gold Coast maintain that resistance when transferred to other areas in Africa where the tsetse fly abounds.

An experimental test of the possibility of resistance to avian leucosis being maintained in other areas (King *et al.* 5) showed that both resistant and susceptible strains maintained their characteristics in localities over 900 miles from those in which they were bred. Similar evidence has been provided by entries of resistant strains in random-sample tests in different parts of the United States. Some of these have maintained their resistance to leucosis over 3,000 miles from their home bases.

Unfortunately disease resistant strains of animals are not likely to retain their resistance long without continued selection. For that reason the maximum benefits from any demonstration of the feasibility of genetic control are less likely to come from the distribution and multiplication of any one resistant stock than from the encouragement thus afforded to many breeders to develop similar resistant strains of their own. In so doing, they may utilize to advantage the genetic resistance that has been established (by man or by nature) in some species breed, or strain. Thus the desirable qualities of the Zebu have been used to breed both beef cattle suitable for some hot climates and dairy breeds adapted to others. The biological efficiency of the White Leghorn can be utilized anywhere. Strains resistant to leucosis have been found to transmit an appreciable part of that resistance to their progeny from crosses with unselected stock.

Early utilization of resistance With some diseases the process of developing a high level of resistance is likely to be a slow

one, particularly since one must select for productivity as well as for resistance In other cases some beneficial results have been obtained without much selection Cameron's method for controlling brucellosis in swine (see Chapter V) is a case in point By a simple test resistant animals are dif ferentiated from susceptible ones and the former are isolated to set up a disease-free herd. Those animals in turn beget offspring with better than average resistance, although peri odic testing is still necessary to keep the herd free

Breeding animals adapted to their environments Apart from any deliberate attempts to breed animals resistant to some infectious disease considerable benefits can be obtained, and some of them very quickly by utilizing animals that are suited to certain adverse environments.

Sometimes even simple mutations can provide a biological advantage. For example both in Canada and in Russia where cold winter temperatures can cause damage to fowls from frozen combs, poultry breeders have deliberately in corporated in special breeds the genes *P* (pea comb) and *R* (rose comb) Together these produce a small walnut" comb that is less likely to freeze than other types.

Regions subject to brilliant sunshine call for the animals best adapted to such conditions. In general colored skins are better protection than white ones for such areas. Mutations that cause photosensitivity might not be serious in cool, cloudy places but could not be tolerated in sunny ones. Similarly breeders of Hereford cattle in areas with much brilliant sunshine should select for the ring of pigment around the eye that prevents trouble from the lesions often found in animals with entirely white heads.

In some cases types that have special protection against an adverse environment carry also other advantages. The Zebu

cattle, with their toleration of high temperatures and resistance to tick borne diseases and tuberculosis, provide a familiar example. At the Mara Experiment Station in the Transvaal Bonsma (1) found mortality up to five years of age from all causes in Africanders (Zebu) European breeds, and their crossbred progeny to be 11 35 and 14 per cent, respectively

Another instance of combined resistance to disease, adaptation to a special environment, and economic desirability is seen in the F generations from crosses between different strains of the fowl. As Goodwin *et al* (3) have conclusively shown, hybrids from such crosses are consistently more resistant to respiratory diseases than are the pure strains that contribute to the crosses. If hybrid vigor is desirable to provide such resistance it is equally valuable for the higher egg production that frequently goes with it. To supply both of these economically important attributes, at least one firm of poultry breeders is now distributing a strain cross which is said to be more adaptable than others that were tested to conditions in southern California, where respiratory diseases make all the difference between profit and loss on many a poultry ranch.

In various parts of the world, particularly in the tropics, the unimproved native stocks of domestic animals are better adapted to their environment than are the more productive breeds brought in from Europe or America. By thousands of years of natural selection, the indigenous stocks have been made more resistant to disease to heat, and to other adverse conditions than are the newcomers from overseas. Under such conditions a compromise in the form of crossbreds often gives the desired combination of productivity and hardiness. Another possibility one that seems particularly appropriate for domestic fowls, is to raise the productivity of the hardy

native stock. Unfortunately in spite of considerable evidence that egg production body size and egg size of unimproved stock can be quickly improved by selection attempts in that direction have been few in number and on a scale not conducive to good results.

Resistance to enzootic diseases Students and others sometimes ask how the farmer should proceed in attempting to increase genetic resistance to some disease When adequate control by other means is already available at a reasonable cost, special efforts to breed resistant stock may not be justified In other cases, when exposure to some enzootic disease seems inevitable and when other treatments are unknown, unsatisfactory or unprofitable, selection for resistance may prove more profitable than selection for higher productivity or more rapid growth. In such cases the least that the breeder on a small scale can do is to exclude from reproduction those animals showing the disease, and especially those doing so at an early age Any heifer that shows mastitis in her first or second lactation is a poor prospect regardless of her pedigree. The breeder will not reduce the incidence of that disease in his herd by clearing her up temporarily with antibiotics if he retains her progeny in the herd.

It would be still better if he could give preference to the sires and dams that beget resistant offspring, perhaps retaining them for reproduction longer than might otherwise be customary Unfortunately on most farms the number of sires used concurrently even of sheep and swine is small, hence comparisons are difficult, and so is selection of sires that can transmit resistance Similarly progeny tests of dams are not always satisfactory because of the small number of offspring per dam in domestic mammals other than swine With larger flocks and herds, where several sires and many females can

undergo progeny tests under comparable environmental con ditions, breeding for resistance to enzootic disease should be easier and more rapid progress may be expected

Taking mastitis in dairy cattle as an example of a persist ent, enzootic disease, let us see what might be attempted with a new approach to an old problem For years control measures have consisted of assorted procedures to reduce the frequency of the streptococci and staphylococci considered responsible for most mastitis. To that end sanitation and disinfection are the order of the day and these orthodox practices are supplemented by treating infected cows with expensive antibiotics These drugs are effective only so long as they are administered, and after treatment is stopped in fection usually recurs.

On the other hand deliberate attempts to infect cows have made it clear that some are completely resistant others highly susceptible (p. 164) Moreover these differences are genetic. The record in Table 9 (p. 88) shows a remarkable reduction of mastitis resulting from nothing more than mass selection, among females only and for one generation only The need now is to see how much more improvement can be effected with selection preferably for a decade or longer based not only on selection of resistant individuals but also on progeny testing of sires, and perhaps of dams also In such work differentiation of resistant and susceptible cows could be accelerated, as Murphy and Stuart have shown (p. 164) by experimental inoculation Since susceptibility is not an all-or none reaction but increases with age, repeated tests at different ages might be desirable, especially after the first few years of selection, in order to identify the most resistant animals.

This kind of study would seem appropriate for the herds of large dairies, state institutions, and experiment stations.

It should not be too difficult to operate such a program through some of the numerous centers for artifical insemination These would be able to test several sires concurrently and to do so thoroughly by having the susceptibility of their daughters tested on many farms under different conditions of exposure and management. Under such circumstances it should even be possible to identify without deliberate inoculation the sires that transmit desirable degrees of resistance.

In selecting for resistance to mastitis there can be no disregard of the equally important selection for production of milk and butterfat The addition of a third objective to these two usual ones makes it somewhat more difficult of course to find bulls that transmit desirable levels of performance in all three qualities When such sires are found, it would seem desirable to multiply their valuable genes as long as they can reproduce or until better ones are found.

Other enzootic diseases should be studied similarly with procedures adapted to each disease and species. It is not necessary to list here all those for which genetic control might be tried one need only think of those for which other measures seem hardly adequate The list is not restricted to infectious diseases. Genetic susceptibility to bloat has been demonstrated in cattle and a correspondent reports having reduced it by selection in sheep Some kinds of sterility are also of genetic origin. Diseases that strike sporadically provide an opportunity for some selection of resistant stock even though exposure comes only at irregular intervals.

A plea for more and different Plum Islands. On Plum Island, *off the Atlantic coast of the United States,* the U.S. Department of Agriculture has established a special station for research on foot-and mouth disease. It is well isolated, and every possible precaution is taken to prevent pathogenic

organisms from escaping However it is apparently no part of the program of that laboratory to study genetic resistance to foot-and mouth disease.

If such an isolated laboratory can be established for one disease would it not be possible to do the same for others? Perhaps an island is not essential in every case. With some diseases, especially those that seem to be already established in this country it should suffice to have an isolated station perhaps somewhere in the western plains. If no animals were distributed from it and if other precautions were taken such a laboratory could test the feasibility of breeding genetically resistant stock.

It would seem particularly desirable to do this with diseases for which methods of treating individual animals and of protecting them against infection are unsatisfactory or unknown In that class belong some of the diseases so recently recognized in the United States that authorities are reluctant to admit that they are enzootic. Scrapie will serve as an example. This disease of sheep so called because the affected animals scrape their itchy skins against fences, walls or buildings has reportedly been found in no less than 17 states of the United States and also in Canada. No treatment is known, and pathologists are not even agreed on the cause As there are no tests by which affected animals can be identified before they show symptoms the procedure in North America has been to slaughter the entire flock whenever one of its members is diagnosed as having the disease. In addition, any exposed sheep sold from such a flock are traced to *their new homes and slaughtered. A careful watch is then* kept on the second flock

In the British Isles, where scrapie has been known for almost two centuries, the actual mortality rate from that disease is probably not more than 1 to 2 per cent (Parry 6).

Losses among older ewes may occasionally run up to 5 per cent a year This indicates that the great majority of the sheep there are already highly resistant to scrapie. As that has been accomplished almost entirely by natural selection there is little doubt that with better procedures particularly the progeny testing of rams, the proportion of genetically resistant animals could be raised still higher

Indications that susceptibility to scrapie is genetically de termined are seen in its high incidence in some flocks, and in certain families within flocks, as noted by Bosanquet *et al* (1) The fact that some sheep show no sign of the disease until they are over three years old makes difficult both the recognition of genetic resistance and selection for it. Any means of identifying genetically susceptible animals at younger ages would be helpful

In spite of this difficulty Parry (6) recommends control of scrapie by the elimination of susceptible strains. After sev eral years study of the disease and with some 6,000 fully recorded sheep under his supervision he writes (7) All our information suggests that the widespread slaughter pol icy is unnecessary and that selective disposal of individuals related to affected animals is all that is required

This statement is remarkably similar to the conclusion of Fortner with respect to control of erysipelas in swine (p. 75) It is worth pointing out that neither of these authorities is a geneticist by profession or training Both are veterinar ians In both cases their researches have led them to recognize the feasibility of genetic control of the particular disease that they have studied

And now to the plea. At Drumheller in Alberta Canada a flock of 500 purebred Suffolks was slaughtered in 1956 be cause some of its members had shown scrapie. Presumably that flock was wiped out to prevent spread of the disease to

others However it is probable that over 80 per cent of the flock were genetically resistant to scrapie (Anyone doubting that such a high level of resistance to disease is possible need only recall that approximately 99 per cent of the population of the United States is genetically resistant to paralytic poliomyelitis.) To a geneticist it seems a tragedy that so many biologically fit sheep should be destroyed to protect a few biologically unfit animals in other flocks. If this had been the first and only case of the disease in North America, there would have been some justification, but it now seems probable that, whether we like it or not, scrapie is here to stay

The amount of compensation paid in this case is not known (to me) but it is to be hoped that it was close to the $100,000 at which the flock was valued. Would it be feasible in similar cases (whether in Canada or in the United States) to keep the flock for study and to use the $100 000 to support that work? The owners would be unable to sell breeding stock, but it would seem better to compensate them for that than for the slaughter of their entire flock. At such a 'Plum Island' with pathologists and geneticists collaborating, the feasibility of raising still higher the already high degree of resistance to scrapie could be tested.

In the foregoing discussion scrapie has been used as an example of the kind of disease that merits an attempt at genetic control It may not be a good one Most breeders of livestock and pathologists will know other diseases that might well be studied in other isolated laboratories

Responsibilities There are several reasons why it would seem to be primarily the responsibility of government agencies to determine and to demonstrate what can be done in the way of genetic control of animal diseases. Such agencies now accept responsibility for maintaining animal health by other

means, including embargo detection, slaughter vaccination and precept, and it is desirable that genetic control be utilized along with these other procedures—not against them. Producers of livestock are more likely to accept a new method of control if it is endorsed by those to whom they have always looked for help Breeders operating on a small scale cannot hope for the results obtainable by those who have larger numbers available for selection.

Effective selection against most diseases may depend on special techniques for early differentiation of resistant and susceptible animals on tests permitting recognition of infection at early stages, on procedures for ensuring uniform and optimum exposure, and on special adaptations of the progeny test *It follows that until the trail has been well* charted progress will be made more rapidly by co-operating teams of scientists than by individual breeders.

For these reasons the initiative belongs with the official disease controllers and the experiment stations. After these agencies have evolved satisfactory procedures for raising the levels of genetic resistance, individual breeders will be more likely to adopt this method of controlling disease themselves. This is exactly what has happened with respect to leucosis in the fowl After geneticists at experiment stations had demonstrated the feasibility of raising resistance by selection, private poultry breeders followed suit within a very few years Strain differences in resistance were so evident in the random-sample laying tests that most breeders soon saw the light and made resistance to leucosis a primary objective in their breeding programs.

It is well to remember however that the Santa Gertrudis, an outstanding breed of beef cattle specially adapted to hot climates, was developed, not at an experiment station but on the King ranch in Texas. Any breeder of livestock who

has the animals, the resources and the desire to breed for resistance to disease need not concede to others any monopoly in that field, but unless he gets a special dispensation he would be wise to confine his operations to diseases that governmental veterinarians are not trying to eradicate by slaughter

Most of the disease resistant varieties of grains, fruits, and vegetables are bred in the agricultural experiment stations most are the result of co-operative research by plant breeders and plant pathologists The comparative ease with which these workers can test thousands of seedlings and produce resistant varieties that will breed true makes the animal breeder envious but even the limited record of accomplishments to date shows that he need not despair

A moot question is How long can the resistant strains of the animal breeder maintain their desirable qualities if selection is discontinued after the strains leave his laboratory? Answers are not yet available, but one cannot expect resistance to be retained so long in animals as in self fertilizing, highly homozygous, cereal grains or in potatoes and other plants that can be reproduced asexually For this reason the most valuable contributions of geneticists and their allies in the experiment stations are likely to be not the production of strains of animals for wide distribution but (1) the demonstration that it is feasible to raise resistance to disease by selection and (2) the discovery of the best ways by which other breeders can do so.

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